Simplified approach

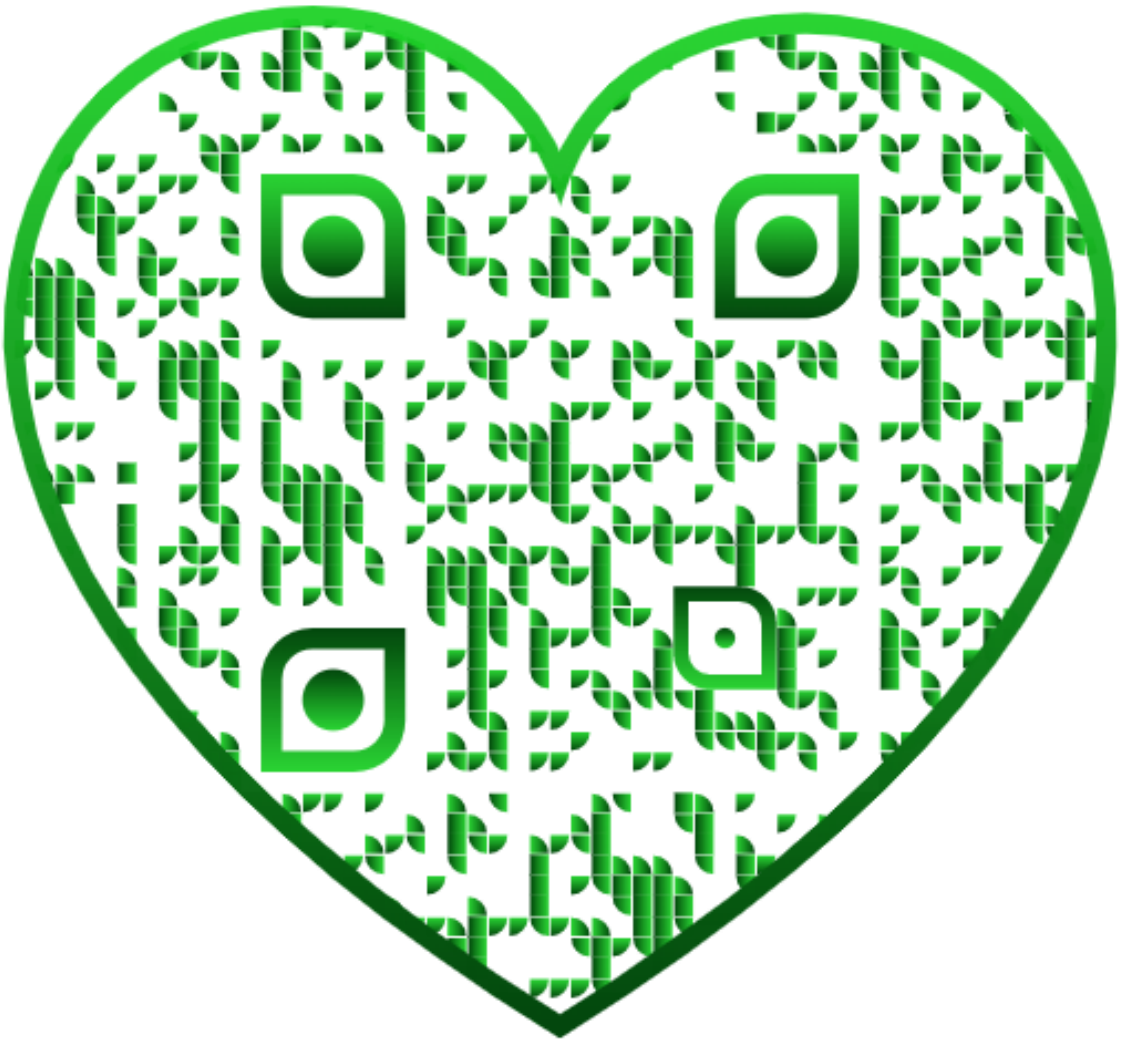
# Mansoura Clinical Pharmacology

## For Medical students

**Edited by**

**Staff members of**
**Clinical Pharmacology Department**
**Faculty of Medicine**
**Mansoura University**

**Volume 2**



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# Preface

Clinical training for undergraduate students often focuses on diagnostic rather than therapeutic skills. Sometimes students are only expected to copy the prescribing behavior of their clinical teachers, or existing standard treatment guidelines, without explanation as to why certain treatment is chosen. Books may not be much help either. Pharmacology reference works and formularies are drug-centered, and although clinical textbooks and treatment guidelines are disease-centered and provide treatment recommendations, they rarely discuss why these therapies are chosen. Different sources may give contradictory advice.

This book in primarily intended for under graduate medical students who are about to enter the clinical phase of their studies. It will provide step by step guidance to the process of rational prescribing together with many illustrative examples. It teaches also skills that are necessary throughout a clinical career. Postgraduate students and practicing doctors may also find it a source of straightforward information.

I wish to acknowledge the ongoing efforts of my contributing authors, and we are deeply grateful to all those who have with such good grace given us their time and energy to supply valuable facts and opinions, they principally include:

- **Prof. Hussein El-Beltagi** who took over the preparation of all books since the 1st edition in 1995 including the revision process, printing control, distribution and selling control.
- **Assist. Prof. Mohamed-Hesham Daba** who took over the revision process and amendments of the last two editions.
- **Assist. Prof. Abdel-Motaal Fouda** who prepared the last two editions in a readable up-to-date text to provide essential information necessary throughout the clinical career.
- **Dr. Sameh Abdel-Ghany** who assisted in the revision process.

Much of any merit this book may have is due to the generosity of those named above.

**Gamal M. Dahab (MD, PhD)**

Professor Emeritus in Clinical Pharmacology
Mansoura Faculty of Medicine

# Mission and Vision

## Our mission

The Clinical Pharmacology Department is seeking excellence and leadership in four major core activities: education, research, community service, and faculty and staff development. We are connecting basic medical sciences with clinical care through innovative and disciplined teaching of clinical pharmacology in an integrative manner

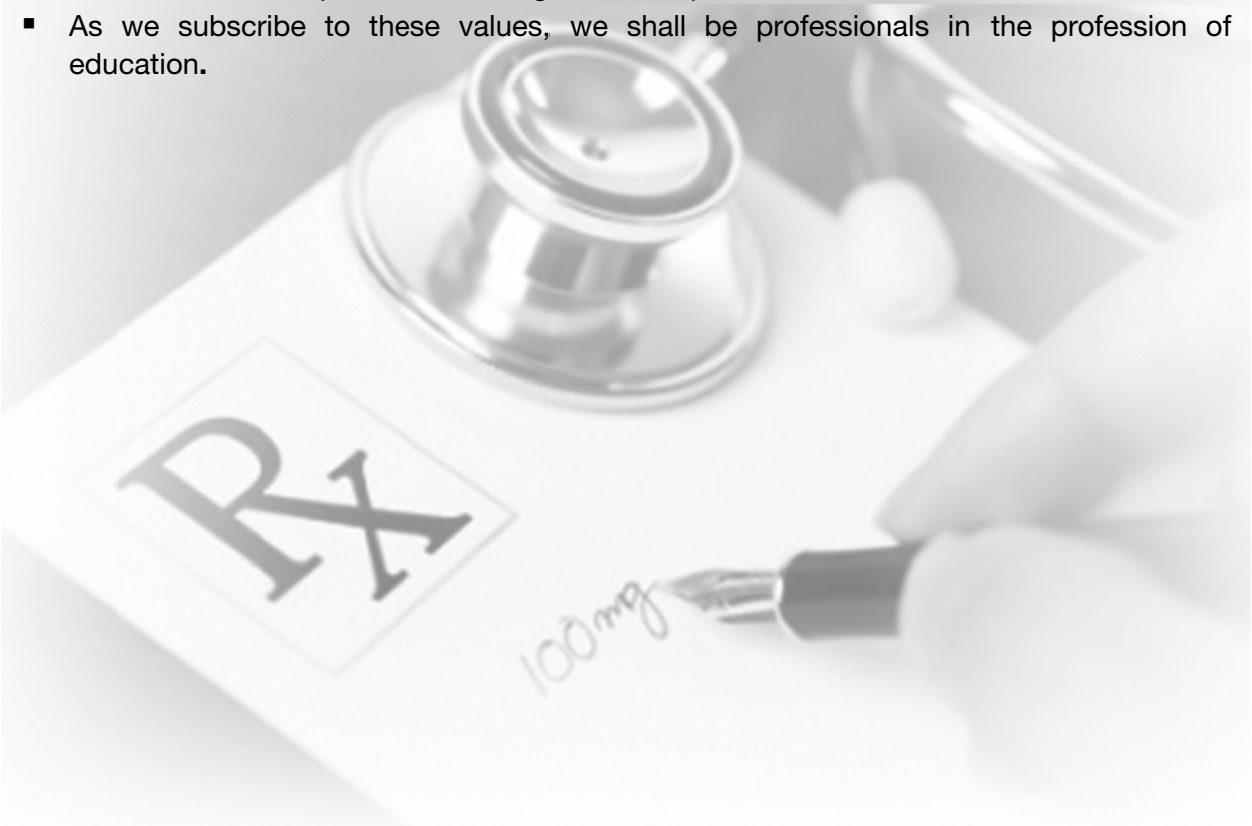
## Our vision

The department of Clinical Pharmacology is aiming to be a premier academic model in the field of pharmacology and therapeutics in Egypt and Middle East through promoting use of the best therapeutics and developing newer experimental and clinical research projects.

## Values

**The guiding principles and beliefs for the department**

- Excellence, creativity, innovation, fairness, honesty, transparency, collaboration, teamwork and lifelong learning
- Recognition that our student comes first
- All members of our department must see themselves as integral to the success of our mission and our department as integral to their personal success.
- As we subscribe to these values, we shall be professionals in the profession of education.



# Contributers

**Effat A. Haroun MD, PhD**
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

**Elhamy M. El-Kholy MD, PhD**
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

**Gamal M. Dahab MD, PhD, MSc** (Int.Med)
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

**Farida M. El-Banna MD, PhD**
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

**Aly M. Gaballah MD, PhD, MSc (**int.Med**)**
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

**Layla T. Hanna MD, PhD**
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

**Mohamed Kheriza MD, PhD, MSc** (Int.Med)
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

**Abdel-Rahman A. Yassin MD, PhD**
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

**Mohmmad A. Attia MD, PhD**
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

**Mohamed Abdel-Ghani MD, PhD**
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

**Hussien M. El-Beltagi MD, PhD**
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

**Karawan M. Abdel-Rahman MD, PhD**
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

**Somaya A. Mokbel MD, PhD**
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

**Amany A. Shalaby MD, PhD**
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

**Amal Abdel-Hamid MD, PhD**
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

**Essam A. Ghyati MD, PhD**
Assist. Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

**Mohamed-Hesham Y. Daba MD, PhD**
Assist. Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

**Abdel-Motaal M. Fouda MD, PhD**
Assist. Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

**Vivian Boshra MD, PhD**
Assist. Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

**Hala A. Al-Ashri MD, PhD**
Assist. Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

**Nageh Rizk MD, PhD**
Lecturer in pharmacology
Mansoura Faculty of Medicine

**Elsayed A. Hassan MD, PhD**
Lecturer in Clin Pharmacology
Mansoura Faculty of Medicine

**Mohamed Abdel-Monem MD, PhD**
Lecturer in Clin Pharmacology
Mansoura Faculty of Medicine

**Mahmoud A. Naga MD, PhD**
Lecturer in Clin Pharmacology
Mansoura Faculty of Medicine

**Ahmad Hassan MD, PhD**
Lecturer in Clin Pharmacology
Mansoura Faculty of Medicine

**Ahlam El-masry MD, PhD**
Lecturer in Clin Pharmacology
Mansoura Faculty of Medicine

**Rehab Hamdy MD, PhD**
Lecturer in Clin Pharmacology
Mansoura Faculty of Medicine

**Mohamed Abou El-khair MD, PhD**
Lecturer in Clin Pharmacology
Mansoura Faculty of Medicine

**Sameh A. Abdel-Ghani MSc.**
Assist. Lecturer in Clin Pharmacology
Mansoura Faculty of Medicine

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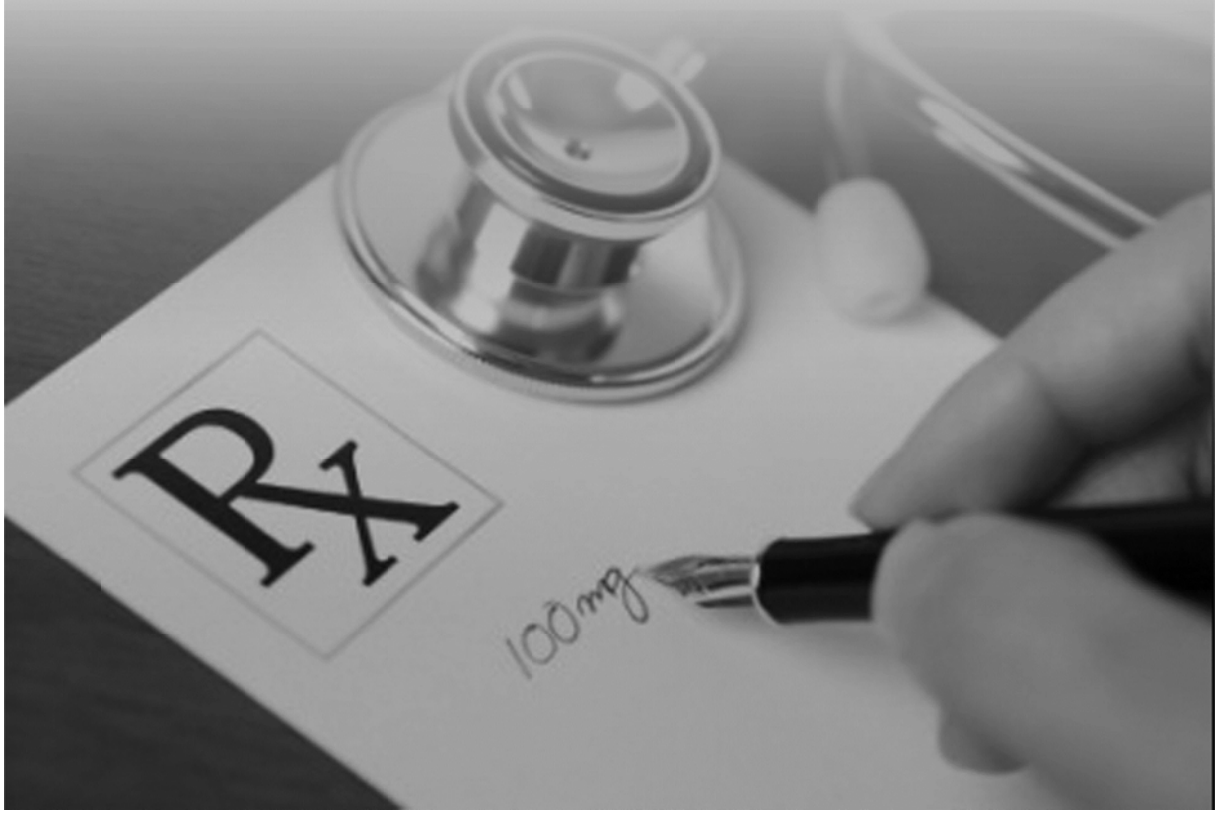
# Chapter 4

# Autacoids And Antiinflammatory Drugs



# Chapter 4

# Autacoids and Antiinflammatory Drugs



## Part 1: Autacoids

**Inflammation** is the complex biological response of vascular tissues to harmful stimuli. Injury produces locally-acting substances that initiate inflammatory response and activate the repair process. These substances are termed **'autacoids'**.

**Examples of autacoids:**

- **Amino acid derivatives:** e.g. histamine and 5-HT (serotonin).
- **Vasoactive peptides:** e.g. angiotensin, kinins and endothelins.
- **Fatty acid derivatives:** e.g. prostaglandins, thromboxanes, leukotrienes, etc.
- **The family of cytokines:** e.g. interleukins, interferones, TNF, growth factors, etc.

### Histamine

- Histamine is formed from the amino acid histidine by the action of *histidine decarboxylase* and stored mainly in **mast cells**. Non-mast cell histamine is found in several tissues including the **brain**.
- No clinically useful drugs affect the synthesis or metabolism of histamine, but certain drugs can cause **release** of histamine from mast cells as a **side effect**.

**Histamine release:** can occur through 2 processes:

- **$Ca^{2+}$ dependent mechanism:** by fixation of IgE to the surface of mast cell with subsequent activation of the complement, this causes $Ca^{2+}$ influx and degranulation of mast cells. Many drugs can induce this type e.g. **penicillin**.
- **$Ca^{2+}$ independent mechanism:**
  - Displacement of histamine from storage granules by **drugs**: e.g. morphine, tubocurarine, vancomycin, and amine antibiotics.
  - Mast cell damage: by venoms, or mechanical trauma.

### Pharmacological effects of histamine

Histamine acts on at least **4** types of receptors:

| R | Postreceptor mechanism | Site | Effect |
|---|---|---|---|
| **H1** | Gq<br>↑ IP3 & DAG | CNS | Functions related to appetite and satiety |
| | | Nonvascular smooth ms | Spasm (→ bronchoconstriction, GIT spasm). |
| | | Blood vessels | – VD of microcirculation (arterioles and precapillary sphincters) → ↑ capillary permeability (edema) and fall of BP.<br>– This VD is due to release of NO from vascular endothelium. |
| | | Exocrine glds | ↑ exocrine secretions (bronchial, lacrimal, etc) |
| | | Sensory nerves | Pain and itching |
| **H2** | Gs<br>↑ cAMP | Gastric parietal cells | ↑ HCl secretion. |
| | | Heart | ↑ cardiac contractility and HR. |
| | | Mast cells | ↓ histamine release (-ve feed back effect). |
| **H3** | Gi<br>↓ cAMP | CNS and presynaptic nerve endings | Wakefulness and modulation of other neurotransmitters release. |
| **H4** | Gi<br>↓ cAMP | Inflammatory cells | Regulation of the inflammatory response |

### Clinical uses of histamine

- Histamine itself has **no** clinical applications.
- Some selective agonists are available for **diagnostic** purposes only e.g. test for gastric secretion.

### Histamine antagonists

- **Physiological antagonists (adrenaline):** adrenaline reverses all the effects of histamine by action on different receptors (see ANS).
- **Histamine receptor antagonists:**
  - $H_1$-blockers: e.g. diphenhydramine, loratidine, etc. (see below)
  - $H_2$-blockers: e.g. cimetidine, ranitidine, famotidine, etc. (see GIT)
  - $H_3$ and $H_4$ -blockers: are not yet available for clinical use.
- **Histamine release inhibitors (mast cell stabilizers): ketotifen** and **cromoglycate** They inhibit $Ca^{2+}$ influx into mast cells and prevent mast cell degranulation.

- **Desensitization therapy (immunotherapy):**
  Immunotherapy is a process in which an allergic patient can become **desensitized** to antigens that trigger allergic responses. Small doses of **the allergic substance** are injected weekly. Each week the dose is increased. Gradually a protective antibody (IgG) is formed to block the allergic reaction. Many patients notice an improvement within 6 months.

## H1-receptor antagonists

| | 1st generation H1 blockers | 2nd generation H1 blockers |
|---|---|---|
| Examples | Diphenhydramine<br>Dimenhydrinate<br>Clemastine<br>Antazoline<br>Cyclizine - Meclizine<br>Chlorpheniramine<br>Promethazine<br>Cyproheptadine | Loratidine<br>Azelastine<br>Cetirizine<br>Fexofenadine<br><br>Ketotifen is a 2nd gen H1 blocker and mast cell stabilizer (see respiratory pharmacology). |
| CNS effects | They can cross BBB (more lipophilic) and exert significant CNS actions | Can**not** cross BBB (less lipophilic) and have little or **no** CNS actions |
| Potency | **Less** potent H1 blockers | **More** potent H1 blockers |
| Effects related to H1 blocking | – Relief of itching, pain and allergic response.<br>– ↓ capillary permeability and inflammatory edema induced by histamine<br>– ↓ bronchoconstriction, bronchial secretions, lacrimation, etc. | |
| Other effects | **Sedation:** but excitation or even convulsions may occur in some cases (especially in children or with high doses).<br><br>**Atropine-like actions:** most of the first generation drugs can block peripheral muscarinic receptors leading to urine retention and blurred vision.<br><br>**Antiemetic action:** useful in preventing motion sickness.<br><br>**α-receptor blocking action:** | Not present |

| | | |
|---|---|---|
| | leading to orthostatic (postural) hypotension in susceptible individuals.<br><br>**5-HT receptor blocking action** *(especially cyproheptadine)*: so it is useful drug for treating carcinoid syndrome. | |
| Duration of action | 3-8 h | 3-24 h |
| Therapeutic uses | ■ **Allergic conditions:**<br>– The use of H1-blockers is effective in allergic conditions in which histamine is the primary mediator (e.g. allergic rhinitis and urticaria).<br>– **N.B.** In bronchial asthma, which involves several mediators, the use of H1-blockers is generally ineffective.<br><br>■ **Motion sickness and vestibular disturbances:**<br>– The first-generation H1-blockers (especially diphenhydramine and promethazine) are effective in preventing motion sickness, but their efficacy in Ménièrs's disease is not established.<br>– They act by blocking H1 and muscarinic receptors in the vestibulocerebellar pathway.<br>– **N.B.** Scopolamine remains the most effective treatment for motion sickness.<br><br>■ **Carcinoid syndrome:**<br>– Carcinoid syndrome is caused by a serotonin-secreting neoplasm of the enterochromaffin cells of the GIT.<br>– When the tumor is not operable, cyproheptadine and other 5-HT blockers can be used to block 5-HT receptors. | |
| Adverse effects | – **Sedation** with impaired concentration**,** but rarely excitation and convulsions may occur in children after toxic doses.<br><br>– **Anticholinergic (atropine-like) actions:** this may cause urine retention, dry mouth and blurred vision. | The **second-generation** drugs are metabolized by the hepatic CYP450 enzymes. Some of the early drugs in this group prolonged the QT interval and caused serious **arrhythmia** (*torsade de pointes*) when given with other drugs that **inhibit** CYP450 system (e.g. **ketoconazole**), and in patients |

| | | |
|---|---|---|
| | – **Orthostatic hypotension** due to their **α**-receptor blocking action**.** | with liver disease. These drugs are now withdrawn from the market. |
| Interactions | These drugs can potentiate the sedative effect of hypnotics, alcohol, etc. | Dangerous **arrhythmia** when given with other drugs that inhibit CYP450 system. |

## Serotonin (5-hydroxytryptamine; 5-HT)

5-HT is formed from the amino acid tryptophane and stored mainly in the **enterochromaffin** tissue of the GIT (90%) and **platelets** (10%). Serotonin is found also as a **transmitter** in many areas within the CNS. Like histamine, no clinically useful drugs affect the synthesis or metabolism of 5-HT, but many drugs can act on 5-HT receptors as agonists or antagonists.

### Pharmacological actions of 5-HT

5-HT acts on at least **7** types of receptors:

| | Distribution | Postreceptor mechanism | Effect |
|---|---|---|---|
| **5-HT$_{1A}$**<br>**5-HT$_{1B}$**<br>**5-HT$_{1D}$**<br>**5-HT$_{1E}$** | CNS, cranial blood vessels | Gi<br>↓cAMP | Role in anxiety, cognitive function, appetite, thermoregulation, memory, nociception<br>VC of cranial BV. |
| **5-HT$_{2A}$**<br>**5-HT$_{2B}$**<br>**5-HT$_{2C}$** | Platelets smooth muscle, CNS | Gq<br>↑ IP3 | Platelet aggregation (5HT$_{2A}$)<br>VC and smooth muscle contraction<br>Hallucinations |
| **5-HT$_3$** | Area postrema, enteric nervous system | $Na^+$ ion channel | Nausea and vomiting<br>Nociception (pain) |
| **5-HT$_4$** | CNS and enteric nervous system | Gs<br>↑ cAMP | ↑ GIT motility and secretions |
| **5-HT$_{5A}$** | CNS | Gi<br>↓cAMP | ? |
| **5-HT$_{6,7}$** | CNS | Gs<br>↑ cAMP | Anxiety, cognitive function, thermoregulation, memory, nociception |

## Some 5-HT agonists and antagonists in clinical use

### 5-HT agonists

- **Buspirone:** (see also CNS)

– It activates central **5-HT$_{1A}$** receptors. It is used for treatment of **anxiety** disorders especially in elderly patients.
– Therapeutic effect may take as long as 2 weeks to appear.

- **Triptans: sumatriptan, zolmitriptan, naratriptan** (see also ANS)

– They activate **5-HT$_{1B/1D}$** receptors.
– The major use of triptans is the treatment of **acute migraine**. Activation of **5-HT$_{1D}$** receptors inhibits inflammation of meninges, pain transmission, and release of VD substances e.g. calcitonin gene-related peptide in trigeminal neurons. Activation of 5-HT$_{1B}$ receptors causes VC of the dilated cerebral vessels. About 50%–80% of patients report relief from pain within 2 hours.
– **5-HT$_{1B}$** activity can cause **coronary spasm** so; these drugs are contraindicated in patients with ischemic heart disease (IHD).

**Serotonin syndrome**

Excess serotonin release in synaptic spaces can cause potentially fatal condition known as "serotonin syndrome". It can occur as a sudden adverse effect of "serotonergic drugs" e.g. MAOIs, tricyclic antidepressants (TCA), selective serotonin reuptake inhibitors (SSRIs), tramadol, meperidine, and buspirone (see CNS).

**Manifestations:** characterized by hypertension, hyperthermia, hyperreflexia, muscle rigidity, diarrhea, and coma.

**Treatment:** sedation with benzodiazepines + 5-HT blockers.

- **Tegaserod:**

– It is a specific **5-HT$_4$** agonist. It increases GIT motility so it is used for treatment of irritable bowel syndrome with constipation.

### 5-HT antagonists

- **Cyproheptadine:**

– It blocks **5-HT$_2$**, **H$_1$**, & **muscarinic** receptors.
– It is used for treatment of symptoms of carcinoid tumor and as antiallergic.

- **Atypical antipsychotics: Olanzapine, risperidone** (see also CNS)

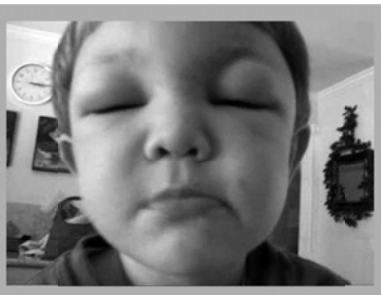
– They block **5-HT$_{2A}$** and dopamine **D$_2$** receptors in the CNS leading to improvement of the negative symptoms of schizophrenia.

- **Ondansetron, granisetron:** (see also GIT)

– They selectively block **5-HT$_3$** receptors centrally (CTZ) and peripherally (GIT).
– It is used for treatment of nausea & vomiting associated with cancer chemotherapy.

## Kinins (bradykinin)

- Kinins are potent vasodilator peptides formed from protein substrates called kininogen by the effect of *kallikrein* enzyme.
- Kinins act on at least **2** subtypes of receptors: **B1** and **B2**. Activation of B2 receptors causes VD and ↑ capillary permeability, smooth ms contraction (bronchoconstriction, GIT colic, etc.), and stimulation of sensory nerves causing pain.
- **Icatibant** is a 2nd generation decapeptide which acts as a **selective antagonist** at bradykinin **B2 receptors.** It is given by s.c. injection for the symptomatic treatment of acute attacks of **hereditary angioedema**. It may also be useful in drug-induced angioedema, ascites, and pancreatitis.
- Recently, a 3rd generation of **orally** active B2-receptor antagonists was developed and currently under study.



**Hereditary angioedema**

HA is a rare autosomal dominant disorder results from deficiency of the C1 esterase inhibitor (C1-INH), a major inhibitor of kallikrein-kinin systems. C1-INH deficiency results in increased formation of bradykinin, which by increasing vascular permeability, causes recurrent episodes of angioedema of the face, airways, GIT, extremities, and genitalia.
HA can be treated with drugs that inhibit the formation or actions of bradykinin.

## Endothelins

- Endothelin is a vasoconstricting peptide produced by the endothelium. There are 3 isoforms. **Endothelin-1** (ET-1) is one of the strongest vasoconstrictors currently studied.
- Endothelins act on at least **2** subtypes of receptors: **$ET_A$** and **$ET_B$.**
- Most of ET-1 effects are mediated through **$ET_A$** receptors present in vascular smooth ms and other tissues. Its activation leads to potent VC, vascular smooth ms proliferation, cardiac hypertrophy, and elevation of blood pressure.
- Increased production of ET-1 has been implicated in a variety of CVS diseases, including primary pulmonary hypertension, cardiac hypertrophy, heart failure, atherosclerosis, and coronary artery disease.
- **Bosentan** is orally active nonselective blocker of **$ET_A$** and **$ET_B$** receptors, while **ambrisentan** is a selective **$ET_A$** blocker. Both drugs are approved for treatment of **pulmonary hypertension**.

## Purines as mediators

Nucleosides (adenosine) and nucleotides (ADP and ATP) are extracellular chemical mediators. ATP is stored in vesicles and released by exocytosis or through tissue damage. Released ATP is rapidly converted to ADP and adenosine. The three purines act on **three** main families of **purine receptors** and exert a wide range of functions.

| R | Postreceptor mechanism | Endogenous ligand | Important sites | Effect |
|---|---|---|---|---|
| **A family** (many subtypes) | G-protein coupled | Adenosine | Lung | Bronchoconstriction |
| | | | Conducting system of the heart | Inhibits conduction |
| | | | Mast cells | Promote mediator release |
| | | | CNS | Complex inhibitory functions |
| **P2Y family** (many subtypes) | G-protein coupled | ATP ADP UDP | Platelets | Promote aggregation |
| | | | CNS | Complex neuropsychiatric effects |
| | | | Other tissue | Still unknown functions |
| **P2X family** (many subtypes) | Ligand gated ion channel | ATP | Stored intracellular | Regulates vascular sm muscle tone and insulin release through $K^+$ channels. |
| | | | Released by damaged tissue | Promote cytokine release by inflammatory cells. |
| | | | Released by nerve terminals | Pain transmission (especially neuropathic pain). |

## Drugs acting on purine receptors:

### Adenosine

It is a short acting purine **A** receptor **agonist**. It is given by **i.v.** route to inhibit AV conduction and converts **supraventricular tachycardia** to the sinus rhythm in non-asthmatic patients (see CVS).

### Methylxanthines

Caffeine, aminophylline and theophylline are purine **A1** receptor **antagonists**. They are used as **bronchodilators** and **CNS stimulants** (see respiratory).

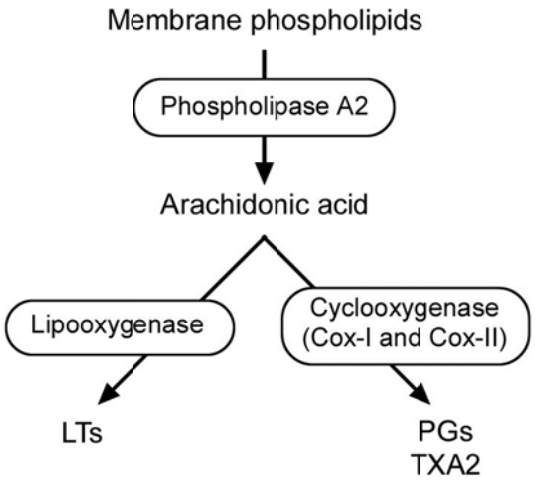
## Fatty acid derivatives (eicosanoids)

They are group of fatty acid derivatives derived from arachidonic acid (20 carbons). The family of eicosanoids **includes:**

### Prostaglandins (PGs)

PGs are members of fatty acid derivatives. All are derived from arachidonic acid by the action of cyclooxygenase (COX) enzyme which has 3 isoforms:

- **COX-1 (physiological; constitutive):** is involved in synthesis of *protective* PGs (e.g. $PGE_2$, $PGI_2$) responsible for protection of stomach from HCl, regulation of RBF, inhibition of platelet aggregation, etc.
- **COX-2 (pathological; inducible):** is involved in synthesis of *undesirable* PGs (e.g. $PGF_{2\alpha}$, $PGD_2$) involved in inflammatory reactions, bronchoconstriction, etc.
- **COX-3 (central):** it is a variant of COX-2 that found only in the **brain** and may be included in synthesis of PGs responsible for fever and pain sensation. It is selectively inhibited by analgesic/antipyretic drugs e.g. **acetaminophen (paracetamol)** and **dipyrone.**




### Thromboxanes (TXs)

- They are also products of cyclooxygenase enzyme.
- They are synthesized in high concentration in platelets.
- They are of 2 forms: **$TXA_2$** (the *active* form) and **$TXB_2$** (the *inactive* form).
- **$TXA_2$** is the most potent endogenous stimulator of *platelet aggregation.*

### Leukotrienes (LTs)

- They are derived from arachidonic acid by the action of *lipooxygenase* enzyme.
- They are of 4 main types: **$LTB_4$, $LTC_4$, $LTD_4$, and $LTE_4$.**
- A mixture of **$LTC_4$, $LTD_4$, $LTE_4$** is termed (the slow-reacting substance of anaphylaxis = SRS-A) that is released during inflammatory response.
- **$LTB_4$** is powerful **bronchoconstrictor** and **chemotactic** for leukocytes.

**Pharmacological actions of eicosanoids**

PGs and other eicosanoids act on cell surface **G-protein coupled receptors**. These receptors are termed DP1-2, EP1-4, FP, etc. The following table summarizes the important effects of different eicosanoids:

| | $PGE_1$, $PGE_2$ | $PGI_2$ | $PGF_{2\alpha}$ | $TXA_2$ | $LTB_4$ |
|---|---|---|---|---|---|
| **BV** | VD | | VC | | VD |
| **Edema** | + | | – | | +++ |
| **Bronchi** | Relaxation | | Constriction | | Severe constriction |
| **Uterus** | Pregnant: contraction<br>Non-pregnant: relaxation | | Contraction | | Contraction |
| **Kidney** | ↑ RBF | | ↓ RBF | | ? |
| **Platelets** | | ↓aggregation | | ↑aggregation | |
| **Other effects** | – ↓ gastric HCl and ↑ mucus secretion<br>– Hyperpyrexia | | | | Chemotaxis |

**Therapeutic uses of prostaglandins**

- **$PGE_1$:**
  - PGE1 (Alprostadil) is still available as urethral inserts for treatment of **erectile dysfunction** in men: it produces VD of the vascular smooth muscle of the corpus cavernosum and improves erection.
  - To maintain patency of the **ductus arteriosus** in infants with congenital cyanotic heart diseases until surgical correction is undertaken. The ductus arteriosus in neonates and infants is highly sensitive to VD by PGE1. Patency of the ductus is necessary in those patients to ensure additional oxygenation of the blood until surgical correction of the problem is undertaken.
  - Treatment of **peptic ulcer**: Mesoprostol is approved for use in patients taking high doses of NSAIDs to prevent gastric ulceration.

- **$PGE_2$:**
  - Induction of **labor near full term** (Dinoprostone).
  - Treatment of **peripheral vascular disease**.

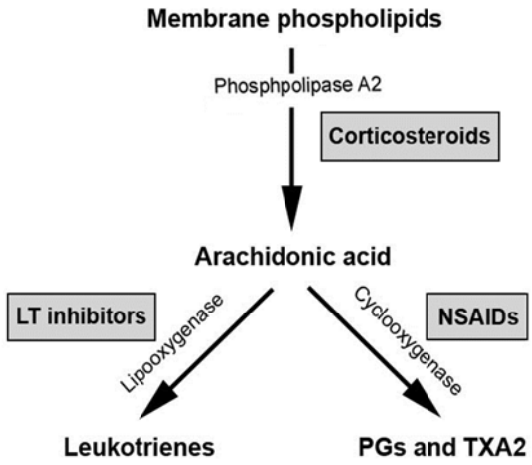
- **$PGI_2$ (Prostacycline):**
  - To **inhibit platelet aggregation** and prevent thrombosis during cardiopulmonary bypass surgery, hemodialysis, and retinal artery occlusion.
  - Treatment of **pulmonary hypertension** and **peripheral vascular disease**.

- **PGF2α:**
  - Induction of **labor near full term** (Enzaprost).
  - **Therapeutic abortion:** as vaginal suppositories. It may be combined with PGE2 and mifepristone (anti-progesterone) to produce more powerful uterine contraction.
  - Treatment of **open-angle glaucoma**: to *dilate* uveoscleral vessels and enhance uveoscleral outflow (↑ drainage) of aqueous humor (Latanoprost).

- **Thromboxanes and leukotrienes:** they have NO current clinical uses.

## INHIBITORS OF EICOSANOIDS

- **Corticosteroids:** they inhibit *phospholipase* $A_2$ enzyme and consequently inhibit synthesis of **ALL** the eicosanoids family (see endocrine pharmacology).




- **Non-steroidal anti-inflammatory drugs (NSAIDs):** they inhibit cyclooxygenase enzyme:
  - **Classical NSAIDs** (e.g. aspirin) inhibit all COX enzyme non-selectively.
  - **Newer NSAIDs** (e.g. celecoxib) inhibit COX-2 selectively.

- **Leukotriene inhibitors:**

**Zafirlukast and Montelukast:**

- They block leukotriene *receptors.*
- They are absorbed orally. Zafirlukast it is given twice daily but Montelukast is given once daily.
- **Uses:** LTs receptor antagonists are new drugs to be used in the treatment of **bronchial asthma** and other inflammatory conditions.

**Zileuton:**

- It inhibits 5-lipooxygenase enzyme leading to decrease LTs *synthesis.*
- **Uses:** treatment of **bronchial asthma** and other inflammatory conditions.

# Part 2: Non-steroidal anti-inflammatory drugs (NSAIDs)

**Classification**

- **Non-selective COX inhibitors (inhibit COX-1 and COX-2):**
  - **Salicylic acid derivatives:** aspirin, aloxiprine, aminosalicylic acid, diflunisal, methyl salicylate, etc.
  - **Acetic acid derivatives:**
    - Carboxylic acetic acid: indomethacin, sulindac, etodolac.
    - Phenyl acetic acid: diclofenac
  - **Propionic acid derivatives:** iboprufen, ketoprofen, fenoprufen, naproxen.
  - **Fenamic acid derivatives:** mefenamic acid, fulfenamic acid.
  - **Pyrazolone derivatives:** phenylbutazone, azapropazone
  - **Oxicams:** piroxicam, tinoxicam.
- **Selective COX-2 inhibitors: celecoxib, etoricoxib, meloxicam.**

## Acetylsalicylic acid (Aspirin)

**Chemistry and pharmacokinetics**

- Oral absorption is complete; most of absorption occurs from the *stomach* and upper GIT.
- Widely distributed to all tissues including CNS.
- Metabolism of salicylates occurs by the hepatic microsomal enzymes.
  - At low doses, elimination is done by the *first-order process.*
  - At high doses, elimination is done by the *zero-order process.*
- Excretion is increased by *alkalinization of urine* (pH 8) because in alkaline urine, most of aspirin is *ionized and less re-absorbable.*

**Mechanism and pharmacological effects**

Aspirin is **non-selective** and **irreversible** COX inhibitor leading to inhibition of both PGs and TXs. This distinguishes it from other NSAIDs, which **reversibly** inhibit COX enzyme.

**Analgesic action:** for mild to moderate intensity pain (not severe pain).

Mechanism:
- Peripheral effect: decrease PGs synthesis in the peripheral inflamed tissues.
- Central effect: decrease PGs synthesis in the subcortical sites (thalamus and hypothalamus).

**Antipyretic effect:**

Aspirin is antipyretic but NOT hypothermic agent i.e. it can lower elevated body temperature but not normal body temperature.

Mechanism:

- Decrease $PGE_2$ synthesis in the hypothalamus.
- Decrease the hypothalamic response to interleukin-1 (endogenous pyrogen).
- Cutaneous VD and increase sweating.

**Anti-inflammatory, anti-immunological and anti-rheumatic effects:**

Mechanism:
By inhibition of COX enzyme, it ↓ synthesis of PGs and TXs, and possibly other inflammatory mediators leading to:

- Decrease inflammatory cell activation and chemotaxis.
- Decrease capillary permeability.
- Decrease hyaluronidase enzyme and inhibits spread of inflammation.
- Stabilize lysosomal membranes of inflammatory cells.

**Respiratory effects:**

- Low toxic doses: produce **metabolic acidosis** → compensatory **hyperventilation** to wash excess $CO_2$ → prolonged respiratory alkalosis.
- High toxic doses: produce metabolic acidosis together with inhibition of RC → death from severe acidosis.

**CVS effects:**

- Therapeutic doses: no significant effect on the CVS.
- Toxic doses: inhibit VMC leading to circulatory failure.

**GIT effects:** salicylates can produce **2 types** of gastric ulcer:

- Acute gastric ulcer: occurs as a result of acute ingestion of large doses of salicylates. The pathogenesis is related to trapping of salicylate ions inside the gastric mucosal cells leading to acute, painful gastric bleeding.
- Chronic gastric ulcer: occurs as a result of chronic ingestion of salicylates. The pathogenesis is related to chronic inhibition of the protective $PGE_1$, $PGE_2$ and $PGI_2$ synthesis leading to chronic ulceration and chronic blood loss.

**Hepatic effects:** salicylates can produce **2 types** of hepatic injury:

- Mild hepatic injury: it is dose-dependent, reversible and asymptomatic. There may be mild increase in serum transaminases (SGOT and SGPT).

– Severe hepatic injury: **"Reye's syndrome":** it is a rare and fatal condition occurs if aspirin is used to control fever of some viral infections (e.g. chicken pox, influenza, etc.) in **children below 12 years old.** There is severe fatty infiltration of the liver, pancreas, and kidney associated with encephalopathy. The etiology is unknown. Management is supportive.

**N.B.**

In children, paracetamol or ibuprofen are considered acceptable substitutes

**Hematologic effects:**

– Antiplatelet action: aspirin inhibit platelet aggregation by:
  – Irreversible inhibition of COX enzyme → ↓ $TXA_2$ → ↓ platelet *aggregation.*
  – Irreversible acetylation of platelet cell membranes → ↓ platelet *adhesions.*
  – Decrease platelet ADP synthesis → decrease platelet *accumulation.*

– Aspirin in high doses (> 6 gm /day) inhibits hepatic **prothrombin** (factor II) synthesis → prolong bleeding time.

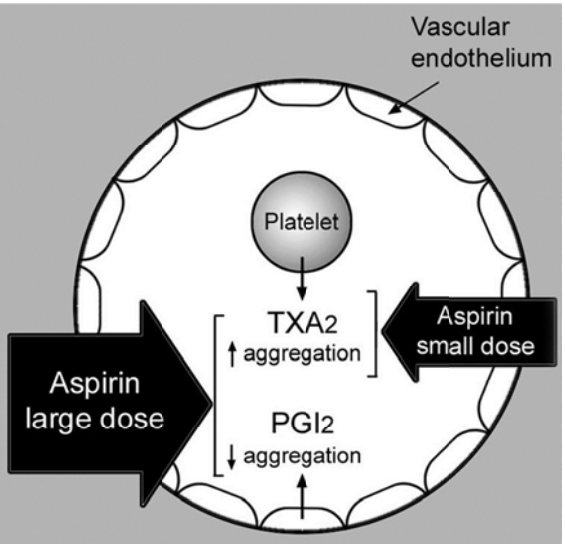
**N.B.**

**Vascular endothelium** produces PGI2 (prostacyclin) that causes VD and inhibition of platelet aggregation

**Platelets** produce TXA2 that causes VC and increase platelet aggregation

**In high doses** (> 300 mg), aspirin ↓ both vascular PGI2 and platelet TXA2.

**In small doses** (75-150 mg), aspirin inhibits only platelet TXA2 synthase enzyme → selective antiplatelet action.




**Q1**: if a patient taking aspirin has to undergo a surgical operation, when must he stop aspirin before the operation?

**A:** he must stop aspirin at least 7 days before the operation because platelet COX-1 is IRREVERSIBLY inhibited (i.e. platelet aggregation is permanently inhibited) and the patient has to synthesize new platelets (life span of platelets is 7-10 days).

**Q2**: if this patient needs urgent operation, what is the next step?

**A:** he must receive fresh blood, or packed platelet transfusion.

**Q3:** if this patient was taking an NSAID other than aspirin, when must he stop this drug before the operation?

**A:** any time because all NSAIDs other than aspirin inhibit COX enzyme REVERSIBLY (i.e. platelet aggregation is not permanently inhibited).

**Renal effects:**

- Analgesic nephropathy: it is chronic renal failure due to chronic abuse of analgesics, which produce chronic renal ischemia due to decrease synthesis of renal $PGE_2$ and $PGI_2$.
- Salt and water retention: due to decrease RBF and increase aldosterone
- Antagonize diuretic effect of diuretics and antihypertensive effects of β-blockers: due to decrease synthesis of $PGE_2$.
- Uric acid excretion: small-to-moderate doses of aspirin can ↓ uric acid excretion and thus contraindicated in patients with gout.

Aspirin in a dose of 75-150mg is not thought to have a significant effect on plasma urate levels - the British Society for Rheumatology recommend it should be continued if required for cardiovascular prophylaxis.

**Metabolic effects:**

- High doses cause uncoupling of oxidative phosphorylation → tachycardia and hyperpyrexia.

**Uterus:**

- Prolongation of pregnancy and delay of labor due to inhibition of PGs necessary for uterine contraction during labor. The use of NSAIDs after 20 weeks of pregnancy is not recommended.

**Therapeutic uses of salicylates**

- **As analgesic and antipyretic:** in mild-to-moderate pain e.g. headache, arthritis, etc. It should not be used routinely as antipyretic because fever may be a normal protective mechanism.
- **As anti-inflammatory and anti-rheumatic:** in rheumatic fever, rheumatoid arthritis, osteoarthritis, etc.
- **As antithrombotic:** see box.

**Who should receive prophylactic low-dose aspirin?**

- All people with established cardiovascular disease (stroke, TIA, ischemic heart disease, peripheral arterial disease).
- All people with target organ damage from hypertension.
- All people with diabetes mellitus who are ≥ 50 years or who have diabetes + hypertension.
- All people aged ≥ 50 years with a 10-year CVS risk score ≥ 20%.

- **As keratolytic and counter-irritant:**
  - Salicylic acid has keratolytic action and is used for treatment of warts.
  - Methylsalicylic acid is used as a counter-irritant for local rheumatic pain.

**Adverse effects of salicylates**

| | |
|---|---|
| **GIT:** | – Epigastric pain, nausea and vomiting.<br>– Acute and chronic gastric ulcers (why?). |
| **Hepatic:** | – Mild reversible hepatic injury in adults.<br>– Severe hepatic injury in children: **"Reye's syndrome".** |
| **Kidney:** | – Analgesic nephropathy (why?).<br>– Salt and water retention.<br>– ↓ the diuretic effect of loop diuretics and antihypertensive effects of β-blockers (why?).<br>– Precipitation of acute gout in hyperurecemic patients. |
| **Blood:** | – Increase bleeding tendency: (why?).<br>– Displacement of other drugs from plasma proteins. |
| **Uterus:** | – Prolongation of pregnancy and delay of labor (why?). |
| **Hypersensitivity reactions:** | – Bronchospasm (aspirin asthma) in patients with history of asthma or allergic rhinitis due to accumulation of LTs. |

**Precautions and contraindications**

- **GIT disorders:** peptic ulcer, gastritis, hemorrhagic pancreatitis, etc.
- **Hemorrhagic disorders:** hemophilia, thrombocytopenia, etc.
- **Chronic renal diseases:** aspirin may aggravate renal failure
- **Chronic liver diseases:** (those patients have bleeding tendency).
- **Uncontrolled hypertension:** risk of fatal bleeding.
- **Gout:** small-to moderate doses may inhibit uric acid excretion.
- **Before surgery:** aspirin must be stopped at least 7 days before surgery.
- **Children <12 years old:** fear of Reye's syndrome.

**Drug interactions**

- Aspirin antagonizes the uricosuric effect of probenecid (see gout).
- Aspirin antagonizes the diuretic effect of diuretics and the antihypertensive effect of antihypertensives (e.g. β-blockers, ACEIs) by inhibition of PGs synthesis.
- Aspirin can **displace** anticoagulants (heparin and warfarin), and other drugs from plasma proteins leading to increase their plasma concentrations.
- Antacids decrease absorption of aspirin.

## Acute aspirin toxicity

Aspirin toxicity is dose-dependent and effects are determined by plasma drug levels

**Manifestations:**

- Tachypnea (hyperventilation) is the **earliest** sign of aspirin toxicity.
- Tinnitus, vomiting, hematemesis.
- Metabolic acidosis.
- Hyperthermia, hypoglycemia, dehydration, and coma.

**Treatment:**

- Repeated gastric lavage with activated charcoal.
- i.v. fluids and sodium bicarbonate to correct dehydration and acidosis.
- Vit K 10 mg i.m. or slowly i.v. to control hemorrhage.
- Alkalinization of urine: to enhance salicylate excretion.
- Hemodialysis in severe cases (when blood levels > 100 mg/dl).

## OTHER NSAIDS

### Diclofenac

- One of the most widely used NSAIDs.
- Generally, it is **less gastric irritant** than other NSAIDs but **more nephrotoxic**. A dose of 150 mg/day can impair renal blood flow and GFR.
- It is often combined with PGE analogue misoprostol to decrease gastric ulceration.
- Topical gel is available for local rheumatic pain and osteoarthritis of the knee and hands.

### Sulindac and ketorolac

- Both have minimal effect on platelet aggregation.
- Sulindac is a **prodrug** and has long t½.
- Ketorolac is a **potent** analgesic but it can cause **severe GIT bleeding**.

### Ibuprofen, fenoprofen, ketoprofen

- They have no reported interactions with oral anticoagulants
- Ibuprofen is a good alternative to aspirin in children with flu fevers.
- Fenoprofen has been reported to induce **nephrotoxic syndrome**
- Long-term use of ibuprofen is associated with an increased incidence of **hypertension** in women.

### Indomethacin

- It is a very potent COX inhibitor but relatively **more toxic** than other NSAIDs.
- It is approved to speed the **closure of patent ductus arteriosus** in premature infants (otherwise it is not used in children); it inhibits the production of PGs which prevent closure of the ductus.

### Piroxicam

- It has long t½ (~ 45 hours).
- Like aspirin and indomethacin, **bleeding** and ulceration are more likely with piroxicam than with other NSAIDs.

### Dysmenorrhea

Dysmenorrhea is a distressing pelvic pain during menstruation. It is common gynecologic complaints.

It can be divided primary (occurring in the absence of pelvic pathology) and secondary (resulting from organic diseases). Primary dysmenorrhea is thought to be due to excessive production of **PGF2α**.

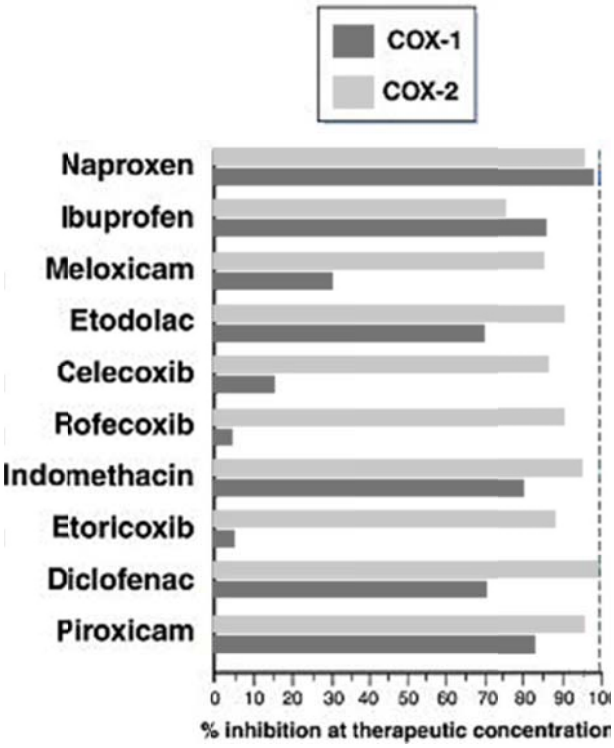
NSAIDs are extremely successful in treatment of both primary and secondary dysmenorrhea. They inhibit PGs synthesis and decrease pelvic congestion.

The FDA approved NSAIDs are in the following order: **diclofenac > ibuprofen > ketoprofen > naproxen.**

**Indomethacin** should be avoided because it has severe adverse effects.

## Selective COX-2 inhibitors:
**Celecoxib, etoricoxib, meloxicam**

Selective COX-2 inhibitors are newer forms of NSAIDs that directly target COX-2 enzyme responsible for inflammation and pain. Celecoxib is approximately 30 times more potent at inhibiting COX-2 than COX-1. Meloxicam is slightly selective for COX-2 than COX-1 enzyme.




Selectivity for COX-2 reduces the risk of peptic ulceration but does not seem to affect other adverse-effects of NSAIDs (especially the risk of renal failure). Selective COX-2 inhibitors may also increase the risk of **cardiovascular accidents** (myocardial infarction, thrombosis and stroke) due to relative increase in $TXA_2$ and platelet aggregation ($TXA_2$ is formed by COX-1 where $PGI_2$ is formed by COX-2). Rofecoxib (Vioxx®) and valdecoxib were withdrawn from the market in 2004 and 2005 respectively because of these potential adverse effects.

| | Non-selective COX inhibitors | Selective COX-2 inhibitors |
|---|---|---|
| **Mechanism:** | They inhibit COX-1 (non-inducible) and COX-2 (inducible) enzymes | They inhibit COX-2 (inducible) enzyme only |
| **Pharmacological effects:** | Both classes have equal analgesic and antipyretic effects | |
| **Gastric side effects:** | Frequent | Less frequent |
| **Renal side effects:** | Frequent | Frequent |
| **Thrombotic complications:** | Decreased (due to *decreased* platelet aggregation) | Increased (due to *increased* platelet aggregation) |
| **Hypersensitivity reactions:** | Frequent | Less frequent |

## Part 3: Acute Rheumatic Fever (ARF)

**Definition:**

It is an inflammatory disease that may develop as a complication of untreated or poorly treated **Group A β-hemolytic streptococcal (GABHS)** infection of the URT. It is caused by antibody cross-reactivity (i.e. autoimmune disease).

**Incidence**

- Age: 5-15 years (rare 2-5 years - never below 2 years).
- Environmental factors: poor living conditions, overcrowding.
- Genetic factors may play a role.
- No sex difference in the incidence or pathogenesis.

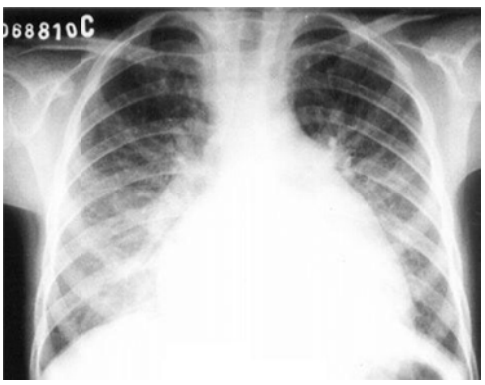
**Etiology and pathogenesis**

**The autoimmune theory (molecular mimicry):** the disease usually follows URT infection with GABHS. This *rheumatogenic strain* contain surface antigens *(hyaluronic acid, cell wall polysaccharides, M protein, etc.)* that are immunologically similar to some host's tissue. Antibodies formed against these antigens will later on **cross-react** with connective tissue antigens in the heart, synovial membranes, caudate nucleus, skin and subcutaneous tissue. **Repeated** streptococcal infection is required for **sensitization** of the immune system.

**Clinical manifestations: "Jones criteria first published 1944":**

**Major criteria:**

- Polyrthritis (70%): the joints are swollen and tender. It is fleeting (migratory), affects large joints, and subsides without deformity.
- Carditis (50%): murmurs, arrhythmia, cardiomegaly, pericardial rub.
- Rheumatic chorea (10%): jerky limb movements and emotional instability occur more in girls. It is reversible.
- Subcutaneous nodules (5%): painless nodules beside muscle tendons.
- Erythema marginatum (1%): red patches over the limbs and trunk.

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**Minor criteria:**

- Fever.
- Arthralgia: pain in the joint.
- ↑ PR interval in the ECG.
- ↑ antistreptolysin O titre (ASO).
- ↑ C-reactive protein and ESR.

**Diagnosis: Revised Jones criteria (1992 update):**

At least **2 major** criteria must be present **OR 1 major + 2 minor** criteria **PLUS evidence** of previous streptococcal infection:

- History of pharyngitis confirmed by positive throat culture for GABHS.
- Elevated **ASO titer > 400 U** or other streptococcal antibodies.

**Management**

**TREATMENT OF THE ACUTE EPISODE**

- **Bed rest:**
  - **2** weeks in absence of carditis.
  - **4** weeks in presence of carditis.
  - **8** weeks in presence of heart failure or cardiomegaly.

**N.B.**
The most dangerous manifestation is **carditis** because it always leads to permanent valvular lesion
*"Rheumatic fever licks the joint but bites the heart".*

- **Diet:** Salt and fluid restriction in presence of carditis or heart failure to avoid volume overload.

- **Antibiotics:** to eradicate streptococcal infection
  - First choice: *benzylpenicillin* (**1** million IU/6h i.v. or i.m.).
  - Second choice (in penicillin allergy): *Co-trimoxazole or erythromycin.*

- **Anti-inflammatory drugs:** to suppress acute inflammation

**A. RF without carditis: salicylates (aspirin)**
**Dose:** 100 mg/kg/d for 2 weeks (till clinical manifestations subside) then give 75 mg/kg/d for 2 weeks then 50 mg/kg/d for another 2 weeks (Max 16 tabs/d).
- Rapid breathing **(tachypnea)** is the **earliest sign** of aspirin toxicity.
- Naproxen is an alternative for patients who are allergic to aspirin.

**B. RF with severe carditis: corticosteroids (prednisolone)**
**Dose:** 2 mg/kg/d for 2 weeks (till clinical manifestations subside) then reduce the dose to 1mg/kg/d for one month.

**Why corticosteroids, but not aspirin, in presence of carditis?**

- Aspirin produces excellent symptomatic relief of arthritis and fever but exerts non-specific effect on carditis.
- Aspirin cannot prevent pericardial rub or valve deformity, but steroids can prevent them.
- High doses of aspirin increase myocardial $O_2$ consumption and heart work and so precipitate valvular lesions and CHF.

## TREATMENT AFTER THE ACUTE EPISODE (PREVENTION OF RECURRENCE)

- **Long-acting penicillin:** *benzathine penicillin.*
  Dose: 1,200,000 IU / 3-4 weeks by deep i.m. injection

**Duration of prophylaxis?**

- For mild or no carditis → *for 3 years from last episode.*
- For moderate carditis → prophylaxis *till 21 years.*
- In severe carditis or recurrent episodes of RF → lifelong prophylaxis.

**Precaution during treatment of ARF with other disease**

| | |
|---|---|
| **ARF with TB** | – Avoid using corticosteroids because they are immunosuppressant and cause flaring of TB infection.<br>– If it is necessary to use corticosteroids, it must be used under umbrella of antituberculos drugs. |
| **ARF with CHF** | – Fluid and salt restriction<br>– If digoxin is needed, use with caution to avoid arrhythmia (the heart is very sensitive to digoxin during Rh activity). |
| **ARF with diabetes** | – If corticosteroids are mandatory, consider adjusting the insulin dose to avoid hyperglycemia.<br>– Consider possible interaction of salicylates with other antidiabetic drugs. |
| **ARF with peptic ulcer** | – Give salicylates through multiple routes or as enteric coated preparations to avoid gastric irritation.<br>– Give salicylates after meals with plenty of fluids.<br>– Use H2 blockers or proton pump inhibitors. |

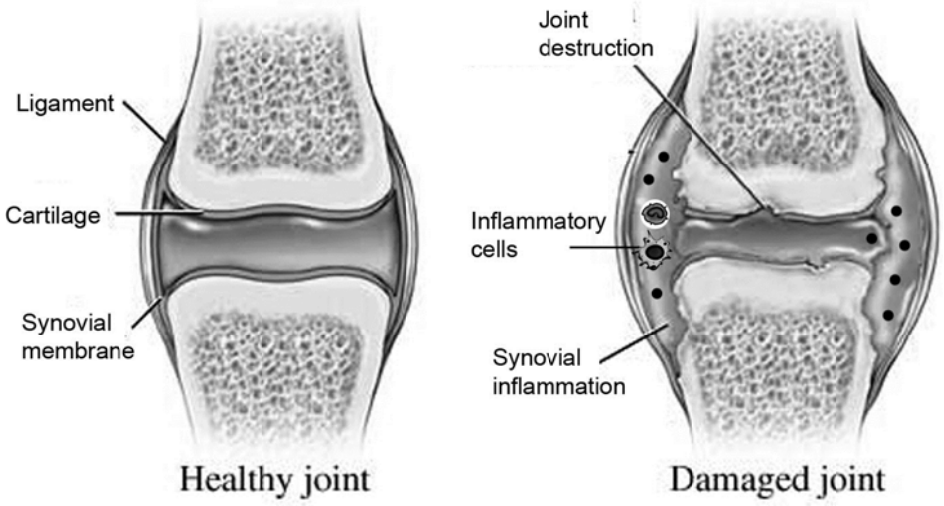
## Part 4: Drug therapy of rheumatoid arthritis (RA)

### Definition

RA is a chronic inflammatory disease characterized by symmetric small joint inflammation, swelling, and deformity. Extra-articular manifestations are also common.

### Pathophysiology

The exact aetiology is unclear however; genetic factors play an important role. Activated T cells, B cells, polymorphonuclear leukocytes (PMLs), macrophages, and complement system lead to production of soluble mediators (lysosymes, cytokines, e.g. TNF-α, IL-1, etc.) that cause joint inflammation, cartilage destruction, bone erosion, and deformity. Why the immune system attacks the joint structures as "foreign" antigens, is unknown.




### Clinical manifestations

- **Articular manifestations:**
  The disease affects mainly small joints of the hands and toes in a symmetrical fashion. In severe cases, large joints are also affected. Affected joints are swollen, painful and with limited mobility. Symptoms are especially worse in the morning. In late cases, characteristic forms of joint deformity are present.

- **Extra-articular manifestations:**
  The spectrum of clinical manifestations of RA can extend to include systemic organs e.g. pleural effusion, pericarditis, anemia, vasculitis, etc.

**Diagnosis**

- **Serological:**
  - Abnormal blood antibodies "rheumatoid factor" can be found in 80% of RA patients.
  - Detection of Cyclic Citrullinated Peptide antibodies (anti-CCP antibodies): more specific than RF and can be detected up to 10 years before the development of RA.
- **Joint X-ray** can show joint swelling and bony erosions typical of RA.

## Management of RA

### Symptomatic treatment

- **NSAIDs:** large doses of NSAIDs are usually required. They offer symptomatic relief of pain and inflammation but don't prevent joint destruction.
- **Corticosteroids:** they are given as short-term therapy till DMARDs give their effect.

### Disease-Modifying Antirheumatoid Drugs (DMARDs)

- They are the most important and should be started as **early** as possible because their effect may take 3 weeks to 3 months to be evident.
- They prevent progression of the disease and slow joint destruction by modifying the immune reactions.
- Combinations of two or more DMARDs are more effective than a single drug.

- **Biologic DMARDs: TNF-α inhibitors**

  TNF-α plays a crucial role in the pathogenesis of RA, and these drugs became the most important DMARDs.

  - **Adalimumab** and **infliximab:** they are monoclonal antibodies that complex with TNF-α and prevent its interaction with T cells and macrophages.
  - **Etanercept:** it is a recombinant protein that interferes with TNF-α and prevents it from binding to its receptors.
  - Acute and chronic infections, live virus vaccination, demyelinating disorders, class III or IV heart failure, and recent malignancies are **contraindications** to the use of TNF inhibitors.
  - Because these drugs are expensive, recent guidelines do not recommend their use until at least one nonbiologic DMARD, usually methotrexate, has been administered without sufficient success.

### ■ Methotrexate

- It is a folic acid antagonist with cytotoxic and immunosuppressant properties. It is one of the first line drugs being used in more than 60% of RA cases.
- It inhibits multiple intracellular enzymes needed for activation of PMLs, T cells, and macrophages.
- It is given once weekly orally. Folic acid 5mg must be given 24h after methotrexate dose to compensate for folic acid deficiency.
- Common **adverse effects**: hepatotoxicity is common (monitoring liver functions is essential), myelosuppression (bone marrow), teratogenicity.

### ■ Hydroxychloroquine (antimalarial drug)

- It decreases synthesis of DNA and RNA in the inflammatory cells and decrease response of T cells to antigens.
- It also stabilizes lysosomal membranes.

### ■ Sulfasalazine

It is metabolized into sulfapyridine and 5-aminosalicylic acid. 5-ASA causes inhibition of IgA and IgM production, and suppresses T and B cell functions.

### ■ Immunosuppressant drugs

- **Cyclophosphamide** and **azathioprine:** suppress immune function by their cytotoxic action through a variety of mechanisms, particularly inhibition of DNA synthesis.
- **Cyclosporine:** It is a potent and specific inhibitor of T cells. It inhibits phosphorylation of calcineurin, a protein that regulates nuclear transcription factors in the T cells.

### ■ Gold salts

Gold salts could be given i.m. or orally. Gold inhibits the functions of human macrophages and decrease the release of inflammatory cytokines and growth factors from inflammatory cells.

### ■ Leflunomide

- It suppresses pyrimidine synthesis and suppresses T cell and B cell functions.
- It is effective as methotrexate in inhibition of bone damage.

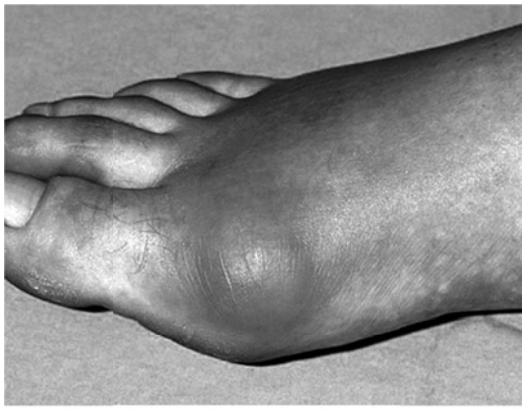
### ■ Anakinra

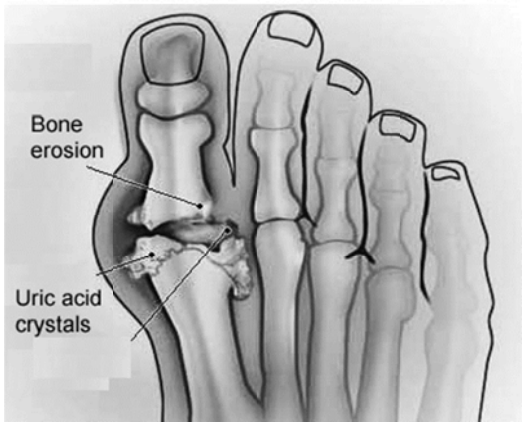
- It is a competitive IL-1 receptor antagonist.
- It has a relatively short half-life and must be administered subcutaneously daily.

# Part 5: Drug therapy of gout

## Basic information

Gout is a form of inflammatory arthritis due to deposition of monosodium urate crystals in the joint tissue. It is caused by chronic hyperuricemia (uric acid > 7 mg/dl = 0.42 mmol/L).






### Biochemistry

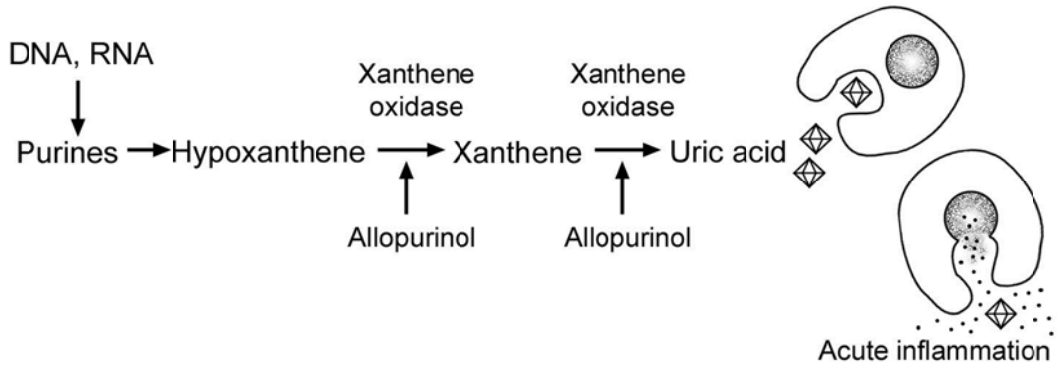
- Uric acid is the end product of purine metabolism by *xanthene oxidase* enzyme.
- The majority of body's uric acid is excreted by the renal PCT. Some drugs (e.g. diuretics) may interfere with excretion of uric acid at this segment leading to its retention.
- The renal excretion of uric acid is enhanced by alkalization of urine.

### Causes of hyperuricemia

- **Decreased uric acid excretion:** account for **90%** of cases of primary gout:
  - Drugs: e.g. diuretics, aspirin, pyrazinamide, ethambutol.
  - Kidney diseases.
- **Increased uric acid production:**
  - High protein diet.
  - During treatment of some hematologic malignancies (e.g. leukemia) due to tissue breakdown (tumor lysis syndrome).
  - Sex-linked uricaciduria (Lesch-Nyhan syndrome).
- **Mixed causes:** alcohol.

### Pathogenesis of gouty arthritis

- When serum uric acid increases, monosodium urate crystals are selectively precipitated in, and around the joint tissue causing irritation and inflammation.
- PNLs and macrophages come and phagocytose the "foreign" uric acid crystals causing swelling and inflammation of the articular tissue.
- Leukocytes eventually die with the release of proteolytic enzymes and inflammatory mediators (e.g. $LTB_4$, IL1, PGs, etc) causing severe inflammation.




**ANTI-GOUT DRUGS**

| **HYPOURICEMIC DRUGS (For CHRONIC gout)** | **ANTI-INFLAMMATORY DRUGS (For ACUTE gout)** |
|---|---|
| **1. ↑ uric acid excretion (uricosuric drugs):** Probenecid, Sulfinpyrazone | 1. Colchicine<br>2. Corticosteroids<br>3. NSAIDs |
| **2. ↓ uric acid synthesis:** allopurinol and thiopurinol | |
| **3. ↑ uric acid metabolism:** uricase enzyme. | |

## HYPOURICEMIC DRUGS

### Uricosuric drugs: Probenecid

**Mechanism of action:** it has biphasic action:

- In **S**mall doses: it *inhibits* tubular **S**ecretion of organic acids (e.g. uric acid, penicillin, rifampin) by inhibiting organic acid transporters in tubular cells.
- In la**R**ge doses (≥500 mg twice/day): it *inhibits* tubular **R**eabsorption of uric acid by inhibiting the urate transporter (**URAT1)**, leading to ↑ excretion of uric acid.

**Therapeutic uses**

- As a uricosuric agent in chronic gout.
- To prolong the t½ of some acidic drugs e.g. penicillin and rifampicin by inhibition of their renal excretion.

**Sulphinpyrazone** is similar to probenecid with added antiplatelet effect due to decrease TXA2.

**Adverse effects**

– Gastric irritation, skin rash, and rarely interstitial nephritis and aplastic anemia.

– If given during the acute attack, it can aggravate the inflammation because rapid lowering of serum uric acid during the acute attack causes mobilization of uric acid crystals from the tissue stores and aggravates the acute inflammation.

**Precautions during the use of uricosuric drugs**

– They should not be used during the acute attack but 2-3 weeks after the acute attack has been subsided.
– Excess fluids and alkalinization of urine help uric acid excretion and prevent stone formation.
– Aspirin may decrease uric acid excretion and antagonize probenecid.

## Inhibitors of uric acid synthesis: Allopurinol

**Mechanism of action**

- Allopurinol is a synthetic purine analogue. It inhibits **xanthine oxidase enzyme** leading to inhibition of uric acid synthesis.
- It has long duration of action because both the parent compound and its metabolite are potent inhibitors of *xanthine oxidase.*

**Therapeutic uses**

- Recurrent attacks of gout (more than 2 attacks per year): the target uric acid level is 5 mg/dl (0.3 mmol/L). Start with 100 mg once daily then gradually increase the dose every 1-2 weeks to reach 300 mg/d.
- As an adjuvant therapy during treatment of hematologic malignancies (e.g. leukemia) to prevent hyperuricemia resulting from tissue destruction.
- Patients with Lesch-Nyhan syndrome should receive allopurinol for life.

**Adverse effects**

– Gastric irritation and hypersensitivity reactions (skin rash).
– Precipitation of acute gout at the start of therapy due to mobilization of the deposited uric acid crystals from tissue stores leading to transient hyperuricemia

  Precautions:

  – Do not give allopurinol during the acute attack of gout.
  – Give prophylactic cover with NSAIDs or colchicine to avoid exacerbation of gout at the start of therapy.

**Drug interactions**

Mercaptopurine, azathioprine, and theophylline are metabolized by xanthine oxidase, and coadministration with allopurinol will dramatically increase levels of these drugs.

## Increase uric acid metabolism: Pegloticase

- Pegloticase is a recent recombinant form of porcine **uricase**, the enzyme that converts uric acid into the water-soluble allantoin.
- It is given as 8 mg i.v. /2 weeks. It can lower serum uric acid within 24 hours. .
- It is indicated in **severe gout** not responding to other agents.

## ANTI-INFLAMMATORY DRUGS

### Colchicine

#### Mechanism of action

- Colchicine is a plant alkaloid. It binds to intracellular **microtubular system** leading to inhibition of leukocyte motility, phagocytosis, and cell division (mitotic blocker).
- It inhibits the release of **$LTB_4$** and other mediators by leukocytes.

#### Therapeutic uses

- Acute attacks of gout:
  - It is specific for gouty arthritis. Other arthritic pains are not relieved by colchicine.
  - It has slower onset than NSAIDs and corticosteroids. Reduction of inflammation and relief from pain occur 12–24 hours after oral administration.
  - Because of its slow onset and high toxicity, it is not a first-choice drug in acute gouty arthritis unless the patient has contraindication for NSAIDs or corticosteroids.
  - The recommended dose is 1.2 mg orally (2 tablets) initially followed by one tablet (0.6 mg)/ 12 hour until the attack resolves.

**Familial Mediterranean Fever (FMF)**

Also known as (recurrent polyserositis) is an autosomal recessive disorder which typically presents by the second decade. It is characterized by recurrent episodes of abdominal pain (due to peritonitis), pleurisy, pericarditis, arthritis. Attacks typically last 1-3 days.

- Familial Mediterranean fever (FMF): by an unclear mechanism.

#### Adverse effects

– **The most common: diarrhea.** Why?
Because the GIT epithelium has rapid rate of turnover. High oral doses of colchicine will inhibit this continuous renewal of GIT epithelium (by inhibiting cell

division) leading to accumulation of toxins and bacterial products with diarrhea.

- **The most rare:** alopecia and myopathy.
- **The most serious:** aplastic anemia and agranulocytosis (bone marrow depression).

## NSAIDs

### Indomethacin and naproxen

- Indomethacin and naproxen are FDA approved NSAIDs for acute gouty arthritis although other NSAIDs can also work (but not aspirin).
- They provide symptomatic relief in acute attacks faster than colchicine.
- Their dose must be reduced if taken with probenecid because probenecid inhibits their renal excretion.

## Corticosteroids

- They are used as anti-inflammatory agents when colchicine and NSAIDs are not sufficient to control the acute attacks or when they are contraindicated.
- For more details about the mechanism, see endocrine pharmacology.

Notes

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## Review Questions

- Mention uses of H1 blockers.
- Mention the main differences between 1st and 2nd generation antihistamines
- Mention the main differences between aspirin and celecoxib.
- Mention the main differences between aspirin and colchicine.
- Mention 2 uses of $PGE_1$, $PGE_2$, $PGI_2$, $PGF_{2\alpha}$.
- Mention side effects of aspirin.
- Mention side effects of colchicine.
- Mention mechanism of aspirin as antiplatelet.
- Mention precautions during the use of antigout drugs.

**Discuss on pharmacological basis each of the following:**

- Aspirin is contraindicated as antipyretic in children with viral infection.
- Aspirin is contraindicated in chronic liver disease.
- Allopurinol is better to be avoided during acute attack of gout.
- Aspirin (low dose) is contraindicated with uricosuric drugs.
- Diphenhydramine is contraindicated in old males with benign prostatic hypertrophy.

**Discuss the pharmacodynamic principles underlying the use of:**

- $PGI_2$ during extracorporeal shunt operations (e.g. hemodialysis).
- $PGI_1$ during surgical correction of patent ductus arteriosus.
- Colchicine in acute gouty arthritis.
- Methotrexate in rheumatoid arthritis.

**Mention the rationale of the following combinations:**

- Mesoprostol is advised with diclofenac (NSAID).
- Colchicine is given before allopurinol in acute gout.

**Of each of the following questions, select THE BEST SINGLE answer:**

**1. Which of the following antihistamines has the LEAST sedation at therapeutic dose?**
**A.** Diphenhydramine
**B.** Loratidine
**C.** Promethazine
**D.** Antazoline
**E.** Cyproheptadine

**2. Cyproheptadine is an antagonist at:**
**A.** $D_1$ and $M_1$ receptors
**B.** $M_1$ and $N_n$ receptors
**C.** $H_1$ and 5-HT receptors
**D.** $H_1$ and $H_2$ receptors
**E.** $\beta_1$ and $\alpha_1$ receptors

**3. Sumatriptan is effective for the treatment of acute migraine by acting as:**
**A.** An antagonist at β adrenergic receptors
**B.** A selective antagonist at $H_1$ receptors
**C.** An inhibitor of prostacycline synthesis
**D.** An agonist at nicotinic receptors
**E.** A selective agonist at 5-$HT_{1D}$ receptors

**4. The pharmacologic effects of acetylsalicylic acid include:**
**A.** Reduction of high body temperature
**B.** Promotion of platelet aggregation
**C.** Reduction of pain by stimulation of PGs synthesis
**D.** Efficacy equals to that of diflunisal as analgesic agent
**E.** Less gastric irritation than other NSAIDs

**5. Aspirin reduces the synthesis of the following eicosanoids EXCEPT:**
**A.** $TXA_2$
**B.** $PGE_2$
**C.** $PGF_{2\alpha}$
**D.** $LTB_4$
**E.** $PGI_2$

**6. All the following are therapeutic uses of prostaglandins EXCEPT:**
**A.** Medical abortion
**B.** To produce uterine relaxation during pregnancy
**C.** Temporary maintenance of the patency of ductus arteriosus in preterm neonates
**D.** Prevention of gastric ulceration caused by NSAIDs
**E.** Treatment of open angle glaucoma

**7. All the following are effects of serotonin EXCEPT:**
**A.** Increased force of cardiac contraction
**B.** Vasoconstriction of the arterioles of the pulmonary and renal beds
**C.** Stimulation of pain response
**D.** Contraction of bronchial smooth muscles
**E.** Relaxation of the GIT smooth muscles

**8. The following statements about NSAIDs are correct EXCEPT:**
**A.** Diclofenac may cause permanent platelet dysfunction
**B.** Indomethacin may cause headache
**C.** Sulindac is a prodrug
**D.** They may impair renal function
**E.** Aspirin may displace coumarin anticoagulants from plasma proteins

**9. The following statements about aspirin are correct EXCEPT:**
**A.** May cause GIT hemorrhage after a single dose
**B.** Enteric-coated tablets cause less gastric bleeding
**C.** May cause metabolic alkalosis in high doses
**D.** May cause Rye's syndrome in children
**E.** Its toxicity may require treatment with hemodialysis

**10. In the treatment of acute rheumatic fever:**
**A.** Aspirin is used to suppress rheumatic carditis
**B.** Polyarthritis never resolve without residual deformity
**C.** Rheumatic chorea requires intensive therapy with corticosteroids
**D.** Benzathine penicillin is used to prevent recurrent streptococcal infections

**E.** Erythromycin is considered the first line antibiotic to eradicate streptococcal infection

**11. Which one of the following statements concerning Cox-2 inhibitors is correct:**
**A.** They show greater analgesic activity than traditional NSAIDs
**B.** They show anti-inflammatory activity greater than traditional NSAIDs
**C.** They increase platelet aggregation
**D.** They harm the kidney as do non-selective cox inhibitors
**E.** They are cardio protective

**12. Manifestations of acute salicylate intoxication include all of the following EXCEPT:**
**A.** Hyperpyrexia
**B.** Hyperpnoea
**C.** Hypertension
**D.** Convulsions
**E.** Metabolic acidosis

**13. Which of the following NSAID is used to treat patent ductus arteriosus in neonates:**
**A.** Ketoprofen
**B.** Mefenamic acid
**C.** Celecoxib
**D.** Phenylbutazone
**E.** Indomethacin

**14. Leukotrienes:**
**A.** Are used for inducing labor in pregnant women
**B.** May be inhibited in patients treated with aspirin and similar drugs
**C.** Are produced from amino acids and stored in granules
**D.** May participate as SRS-A in asthmatic or anaphylactic reactions
**E.** LTB4 is powerful platelet aggregator

**15. Drugs used in the treatment of gout include all of the following EXCEPT:**
**A.** Indomethacin
**B.** Allopurinol
**C.** Colchicine
**D.** Probenecid
**E.** Aspirin

**16. In the treatment of gout:**
**A.** Aspirin should be combined with a uricosuric
**B.** Therapy with sulphinpyrazone should be accompanied by high fluid intake and alkalinization of the urine
**C.** Allopurinol will provide useful relief from an acute attack
**D.** Colchicine can be used prophylacticaly to prevent recurrence
**E.** Loop diuretics are indicated to wash the excess uric acid from blood

**17. The following is true about allopurinol:**
**A.** It has short duration of action
**B.** It can act as a uricosuric drug
**C.** It may worsen acute gout
**D.** The parent drug but not its metabolites are xanthine oxidase inhibitors
**E.** Is not recommended for patients treated by anticancer drugs

**18. The following is true about PGF2α:**
**A.** It causes bronchodilatation
**B.** It can be injected in the amniotic sac to induce abortion
**C.** It increases renal blood flow
**D.** It increases platelet aggregation
**E.** It causes hypotension

**19. All the following drugs can decrease platelet aggregation EXCEPT:**
**A.** Ketanserine
**B.** Celecoxib
**C.** Sulphynpyrazone
**D.** Aspirin
**E.** Epoprostenol (prostacyclin)

**20. All the following drugs can be used in the treatment of rheumatoid arthritis EXCEPT:**
**A.** Methotrexate
**B.** Gold
**C.** Leflunomide
**D.** Prednisolone
**E.** Colchicine

**21. The most serious side effect of colchicine therapy is:**
**A.** Agranulocytosis
**B.** Diarrhea
**C.** Alopecia
**D.** Amyloidosis
**E.** Anorexia

**22. Which one of the following drugs could significantly impair the ability to drive an automobile?**
**A.** Diphenhydramine.
**B.** Ergotamine.
**C.** Fexofenadine.
**D.** Ranitidine.
**E.** Sumatriptan.

**23. Which one of the following is an action of colchicine?**
**A.** It produce uricosuria
**B.** It produce constipation
**C.** It produce polycythemia
**D.** It stimulates cell division
**E.** It inhibits leukocyte migration and phagocytosis

**24. Which of the following is a uricosuric agent used in chronic gout?**
**A.** Sulfasalazine
**B.** Sulfinpyrazone
**C.** Allopurinol
**D.** Colchicine
**E.** Chloroquine

**25. Which one of the following drugs acts by blocking interleukin-1 receptors?**
**A.** Anakinra
**B.** Sulfasalazine
**C.** Gold saults
**D.** Methotrexate
**E.** Etanercept

**26. Which one of the following drugs acts by blocking soluble receptors of TNF-α?**
**A.** Anakinra
**B.** Sulfasalazine
**C.** Gold saults
**D.** Methotrexate
**E.** Etanercept

**27. Inflammation is a complex tissue reaction that includes the release of cytokines, leukotrienes, prostaglandins, and peptides. Prostaglandins involved in inflammatory processes are produced from arachidonic acid by:**
**A.** Cyclooxygenase 1
**B.** Cyclooxygenase 2
**C.** Glutathione – S – transferase
**D.** Lipoxygenase
**E.** Phospholipase A2

**28. A 60-year-old woman has glaucoma following cataract surgery. Which of the following can be used to reduce intraocular pressure?**
**A.** Leukotriene LTD4 or its analogs
**B.** Prostaglandin E2 or its analogs
**C.** Prostaglandin F2α or its analogs
**D.** Slow-reacting substance of anaplylaxis (SRS-A)
**E.** Thromboxane A2 or its analogs

**29. A 45-year-old surgeon has developed symmetric early morning stiffness in her hands. She wishes to take a nonsteroidal anti-inflammatory drug to relieve these symptoms and wants to avoid gastrointestinal side effects. Which one of the following drugs is most appropriate?**
**A.** Aspirin
**B.** Celecoxib
**C.** Ibuprofen
**D.** Indomethacin
**E.** Piroxicam

**30. The following drug is considered a mast cell stabilizer:**
**A.** Adrenaline
**B.** Salbutamol
**C.** Cromoglycate
**D.** Loratidine
**E.** Ondansetron

**31. The following drug blocks $5HT_{2A}$ receptors in the CNS and is useful in relieving the negative symptoms of schizophrenia:**

**A.** Buspirone
**B.** Ondansetron
**C.** Cyproheptadine
**D.** Olanzapine
**E.** Alosetron

**32. The toxicity spectrum of aspirin does not include:**
**A.** Increased risk of encephalopathy in children with viral infections
**B.** Increased risk of peptic ulcers
**C.** Hyperprothrombinemia
**D.** Metabolic acidosis
**E.** Respiratory alkalosis

**33. Accidental poisonings are common with both aspirin and ibuprofen, the two drugs are available in tasty chewable tablets. In cases of overdose, aspirin is more likely than ibuprofen to cause:**
**A.** Autonomic Instability
**B.** Hepatic necrosis
**C.** Metabolic acidosis
**D.** Thrombocytopenia
**E.** Ventricular arrhythmias

**34. Which of the following compounds is most likely to lower circulating levels of leukotrienes?**
**A.** Zileuton
**B.** Montelukast
**C.** Ibuprofen
**D.** Aspirin
**E.** Allopurinol

**35. The action of aspirin that results in its greater efficacy as an antithrombotic (anti-platelet) drug is its ability to**
**A.** Inhibit lipoxygenase as well as cyclooxygenase
**B.** Selectively inhibit cyclooxygenase I
**C.** Inhibit leukocyte migration
**D.** Promote uric acid excretion
**E.** Acetylate cyclooxygenase

**36. Which of the following statements best describes the usual course of rheumatoid arthritis?**
**A.** It is an acute exacerbation of joint pain treated with short-term anti-inflammatory therapy
**B.** It is a chronic disease characterized by acute changes within nonsynovial joints
**C.** It is an acute disease that is characterized by rapid synovial changes due to inflammation
**D.** It is a chronic disease characterized by acute exacerbations followed by remissions with consequences associated with chronic inflammatory changes
**E.** It is a joint disease characterized by a marked loss of calcium from the bones and a resultant thinning of the bones

**37. All of the following statements concerning an acute gouty arthritis attack are correct EXCEPT**
**A.** The diagonosis of gout is assured by a good therapeutic response to colchicine because no other form of arthritis responds to this drug
**B.** To be assured of the diagnosis, monosodium urate crystals must be identified in the synovial fluid of the affected joint
**C.** Attacks frequently occur in the middle of the night
**D.** An untreated acute attack may last up to 2 weeks
**E.** The first attack usually involves only one joint, most frequently the big toe (first metatarsophalangeal joint)

**38. TNF- α is an example of:**
**A.** Eicosanoids
**B.** Interleukins
**C.** Cytotoxic factors
**D.** Interferons
**E.** Colony stimulating factors

**39. Potential adverse effects associated with aspirin include all of the following EXCEPT**
**A.** Gastrointestinal ulceration
**B.** Renal dysfunction
**C.** Enhanced methotrexate toxicity
**D.** Cardiac arrhythmias

**E.** Hypersensitivity asthma

**40. The cyclooxygenase isoenzymes COX-1 and COX-2 differ from each other in that:**

**A.** They catalyse different pathways in prostanoid biosynthesis
**B.** COX–1 is inhibited by aspirin but not COX–2
**C.** COX–2 is inhibited by ibuprofen but not COX–1
**D.** COX–1 is constitutive while COX–2 is inducible
**E.** COX–2 is essential for renal function

**41. Which one of the following drugs is a selective inhibitor of central COX-3 in the brain?**

**A.** Paracetamol
**B.** Ibuprofen
**C.** Aspirin
**D.** Celecoxib
**E.** Colchicine

**42. Irritable bowel syndrome with constipation can be treated by:**

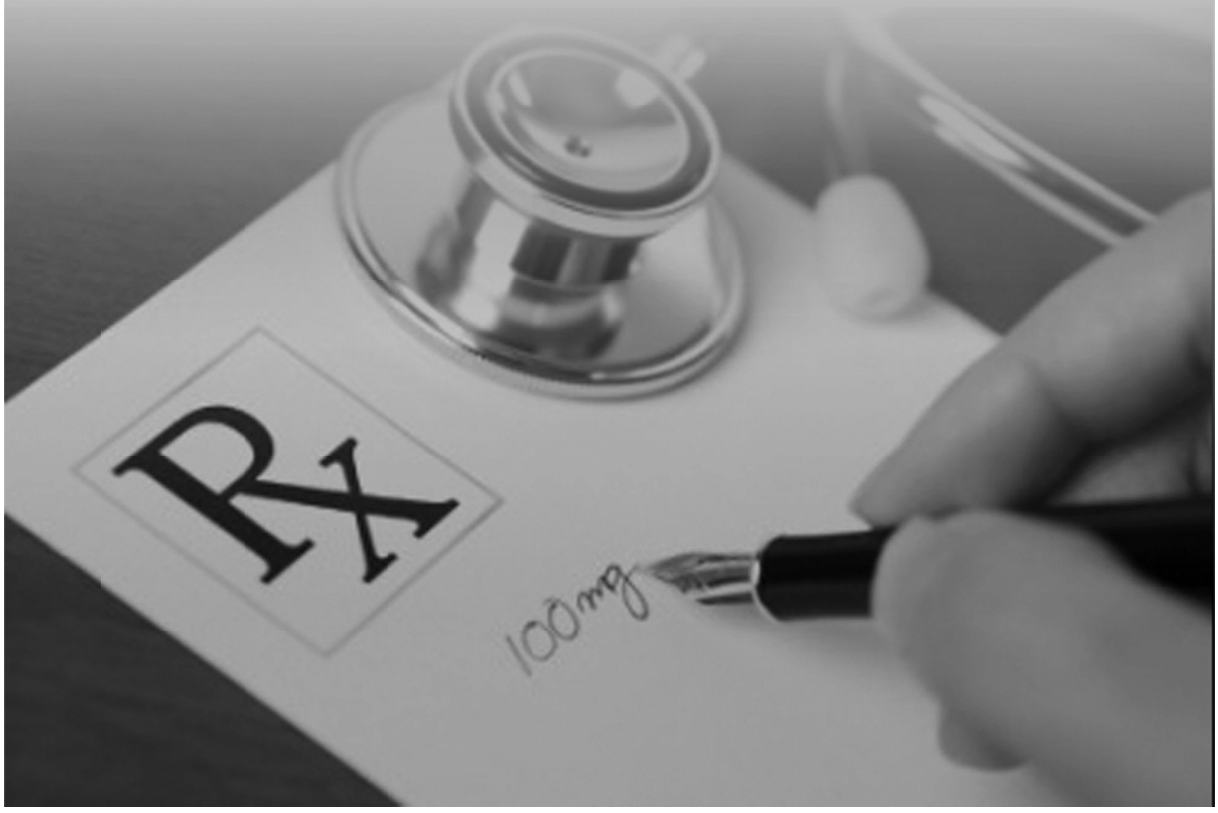
**A.** Alosetron
**B.** Tegaserod
**C.** Ondansetron
**D.** Olanzapine
**E.** Buspirone

**Answers**

| | | | | |
|---|---|---|---|---|
| 1 B | 11 C | 21 A | 31 D | 41 A |
| 2 C | 12 C | 22 A | 32 C | 42 B |
| 3 E | 13 E | 23 E | 33 C | |
| 4 A | 14 D | 24 B | 34 A | |
| 5 D | 15 E | 25 A | 35 E | |
| 6 B | 16 B | 26 E | 36 D | |
| 7 E | 17 C | 27 B | 37 D | |
| 8 A | 18 B | 28 C | 38 C | |
| 9 C | 19 B | 29 B | 39 D | |
| 10 D | 20 E | 30 C | 40 D | |

# Chapter 5

# Cardiovascular Pharmacology



# Chapter 5
# Cardiovascular Pharmacology



## Part 1: Systemic hypertension and antihypertensive drugs

### Basic information

#### Vascular smooth muscle contraction and relaxation

**Vasoconstriction** is initiated by opening of voltage gated L-type **$Ca^{2+}$** channels in the membrane of vascular smooth muscle cells. Increased intracellular **$Ca^{2+}$** triggers the phosphorylation of *myosin light chain kinase* which initiates contraction.

**Vasodilation** is initiated by either:

- Activation of guanylyl cyclase → **↑cGMP** → dephosphorylation of *myosin light chain kinase* → smooth ms relaxation.
- **Opening of $K^+$ channels** in the vascular smooth muscle cell membrane → smooth ms stabilization (hyperpolarization) → relaxation.

#### The vascular endothelium and local vasomotor control

Beside the neural control of blood vessels through the sympathetic and parasympathetic systems, the **vascular endothelium** produces various compounds that help controlling the vascular tone:

| | |
|---|---|
| **Nitric oxide (NO; or EDRF)** | It is a diffusible gas with very short half-life. It causes **VD** by increasing intracellular **cGMP**. It protects against atherosclerosis, high blood pressure, heart failure and thrombosis. |
| **PGI2** | It is synergistic to NO. It causes **VD** via specific receptors |
| **Endothelin** | Is a 21-amino-acid peptide. By its action on $ET_A$ receptors, it causes severe **VC** and vascular smooth muscle **hypertrophy**. |

| | |
|---|---|
| **Angiotensin-converting enzyme (ACE)** | Located on the endothelial cell membrane and converts circulating angiotensin-I (synthesized by the action of renin on angiotensinogen) to angiotensin-II. By its action on AT1 receptors, Ang-II causes **VC** and stimulates **aldosterone** release. |
| **Other factors** | **Histamine** causes VD, **bradykinin** (synthesized from kininogen) causes VD, and **serotonin** (released by platelets) causes VC. |

## Management of systemic hypertension

**Systemic hypertension** is persistent elevation of BP above 140/90.

**Classification of hypertension:**

- According to etiology: primary (= essential, 90%) or secondary.
- According to type: systolic, diastolic, or mixed.
- According to degree: see table.

**Classification of blood pressure levels of the British Hypertension Society**

| Category | Systolic BP (mmHg) | Diastolic BP (mmHg) |
|---|---|---|
| **Normal blood pressure** | <140 | <90 |
| **Hypertension** | | |
| Stage 1 (mild) | 140–159 | 90–99 |
| Stage 2 (moderate) | 160–179 | 100–109 |
| Stage 3 (severe) | ≥180 | ≥110 |
| **Isolated systolic hypertension** | >140 | <90 |

**N.B.** If systolic and diastolic BP fall into different categories, the higher value should be taken for classification.

**Target BP:**

- For most patients, the **goal of therapy** is to maintain BP **< 140/90** mm Hg.
- In patients with **DM** or **chronic kidney disease**, BP should be **< 130/80** mm Hg.

**Non-drug therapy = life style modification:**

- Dietary **sodium** restriction and **potassium** and magnesium supplementation.
- Stop **smoking** and avoid **stress**.
- **Weight** reduction alone can correct hypertension in 75% of obese patients.
- Daily physical **exercise** (~30 min/day): it lowers serum cholesterol, improves endothelial functions, and enhances tissue oxygenation.

- Control of **risk factors**: e.g. diabetes mellitus, hyperlipidemia, and obesity.
- Avoid **drugs** that ↑ BP e.g. sympathomimetics, sodium-containing drugs, oral contraceptive pills, corticosteroids.

**N.B.** Patients failing to normalize BP after **2 weeks** of non-pharmacological therapy should be considered for drug therapy.

### Drug therapy (antihypertensive drugs):

| First choice groups (commonly used drugs) | Second choice groups (used in special cases): |
|---|---|
| ▪ **A ngiotensin-converting enzyme inhibitors (ACEIs)**<br>▪ **B eta-blockers**<br>▪ **C alcium channel blockers**<br>▪ **D iuretics** | ▪ **$\alpha_1$- blockers:** prazosin and doxasosin.<br>▪ **Combined α and β-blockers:** labetalol.<br>▪ **Adrenergic neuron blockers:** α-methyldopa and reserpine.<br>▪ **Vasodilators: e.g.** hydralazine.<br>▪ **Central $\alpha_2$ stimulants:** clonidine.<br>▪ **Endothelin blockers:** Bosentan.<br>▪ **Dopamine agonists:** fenoldopam. |

## Beta-blockers

**For detailed mechanism and pharmacology: see chapter 2.**

**Indications of beta-blockers in hypertension:**

- Hypertension associated with cardiac problems e.g. IHD, cardiac arrhythmia, aortic dissection, etc.
- Hypertension associated with thyrotoxicosis.
- Hypertenstion associated with increased sympathetic overactivity.

## Diuretics

**For detailed mechanism and pharmacology: see chapter 3.**

**Indications of diuretics in hypertension:**

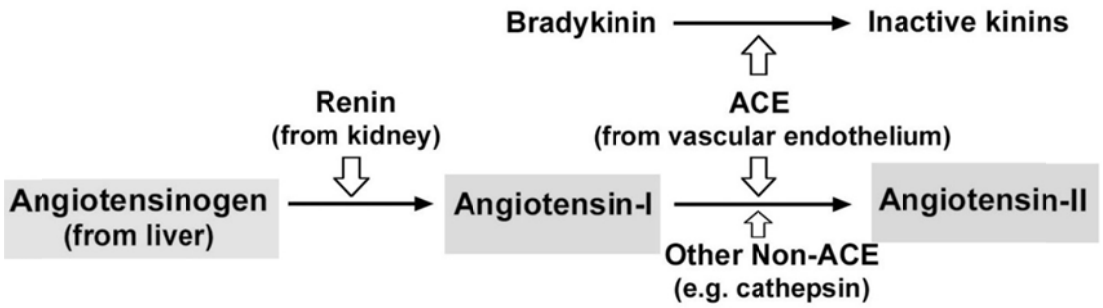
- Thiazides are given as initial therapy in most cases of mild, non-complicated essential hypertension.
- Hypertension associated with volume overload (salt and water retention): e.g. CHF, liver cirrhosis, primary hyperaldosteronism, pulmonary edema, etc.

## Angiotensin-converting enzyme inhibitors (ACEIs)

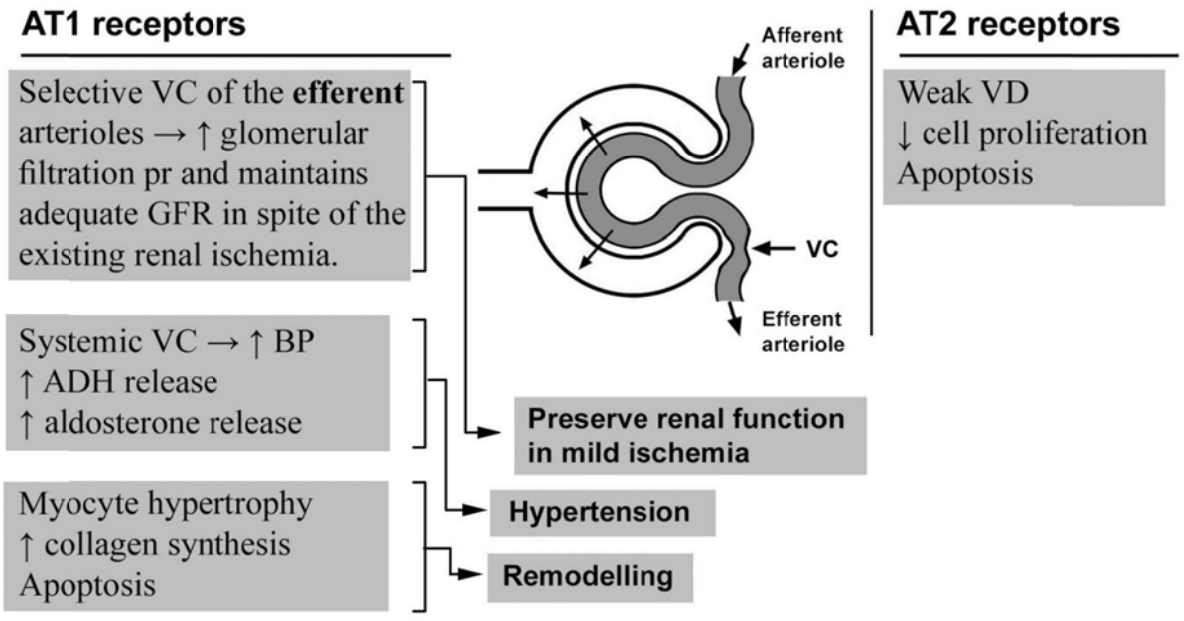
### Background

#### The renin-angiotensin-aldosterone (RAAS) system

- When renal ischemia occurs, there is ↓ RBF and ↓ GFR. This may lead to acute oliguria that may develop to acute tubular necrosis.
- As a compensatory mechanism, **renin** is released from the juxtaglomerular cells of the kidney as a rescue message to initiate stimulation of RAAS as follows:




- Ang-II acts on **AT1** receptors in the **efferent** arterioles of the kidney causing their **VC** and thus maintains adequate GFR in spite of the ↓ RBF.
- Unfortunately, Ang-II acts on AT1 receptors in other vascular beds and tissues causing systemic **VC**, **cell hypertrophy**, and **apoptosis** (i.e. degenerative changes).



**Should we inhibit the RAAS?!**

- Inhibition of the RAAS will correct the hypertension but also will ↓ GFR and aggravate RF if renal ischemia was grave.
- Normal S. creatinine is 0.3-1.2 mg/dl. If S. creatinine is up to **3 mg/dl** (i.e. mild renal impairment) → you can block RAAS.
- If S. creatinine >**3 mg/dl** (i.e. severe renal impairment) → blocking the RAAS is dangerous and will aggravate RF.

**Inhibitors of RAAS**

- Inhibitors of **renin release:** β-blockers, α-methyldopa, and clonidine.
- Inhibitors of plasma **renin activity**: aliskiren.
- Inhibitors of **Ang-2 formation:** ACEIs
- **AT1 receptor blockers** (ARBs) e.g. losartan, valsartan

## Angiotensin converting enzyme inhibitors

### Classification

- **SH-containing drugs:** Captopril, zofenopril, alacepril
- **Non SH-containing drugs:** Enalarpril, fosinopril, lisinopril, benazepril, ramipril

### Pharmacological properties of some ACEIs

| | Captopril | Fosinopril | Enalapril | Lisinopril | Benazepril |
|---|---|---|---|---|---|
| SH group | + | – | – | – | – |
| Immune S/E | + | – | – | – | – |
| Prodrug | – | + | + | – | + |
| Metabolism | Liver, kidney | Liver, kidney | Liver | **No** metabolism | Liver, kidney |
| Onset | 1 – 4 h | | | | |
| Frequency of administration | /8 h | /12 h | /12 h | /24 h | /24 h |
| SL dose | 25 mg | None | None | None | None |

### Mechanism of action

They inhibit **Ang-converting enzyme (ACE)** in the vascular endothelium leading to:

- Inhibition of both **Ang-II formation** and **aldosterone release** (→ ↓ both VC and salt & water retention).
- Prevent degradation of **bradykinin** which is a potent VD.
- Most ACEIs have **direct VD action** to both arteries (i.e. ↓ afterload) and veins (i.e. ↓ preload).

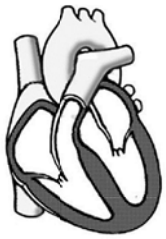
### Pharmacological effects

**CVS:**

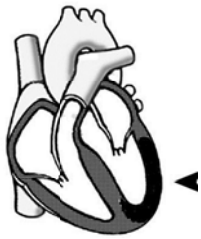
- They ↓ BP mainly by decreasing peripheral resistance **but no reflex tachycardia or changes in the COP can occur**. This may be due to either (1) resetting of baroreceptors; and/or (2) enhanced parasympathetic activity.
- They ↑ **COP** (only in presence of **CHF**) due to reduction of both venous return (preload), and systemic BP (afterload).
- They ↓ myocardial changes complicating acute **myocardial infarction** (ventricular hypertrophy, and dense collagen scar) because they prevent myocyte cell hypertrophy and collagen synthesis **(i.e. prevent cardiac remodeling).**

**Other tissue**

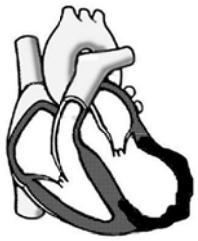
- They ↓ apoptosis, ↓ cell hypertrophy, & ↓ collagen synthesis (i.e. they reduce degenerative changes caused by the action of Ang-II on AT1 receptors).



Normal



MI and necrosis



Ventricular remodeling

Cardiac remodelling means change in the size or shape of the heart due to dilatation, hypertrophy, or excessive formation of collagen scar.

After MI, myocyte cell necrosis triggers stimulation of the RAAS. Ang-II triggers the formation of thick scar and myocyte hypertrophy leading to cardiac remodelling.

### Therapeutic uses

- **Systemic hypertension:**
  - Hyperreninemic hypertension.
  - Normoreninemic hypertension: because they are direct VDs.
- **Congestive heart failure (CHF):**
  - To ↓ afterload and preload through reduction of both systemic vascular resistance, and aldosterone release (↓ Na and $H_2O$ retention).
  - To ↓ myocardial hypertrophy and dilatation (i.e. ↓ remodeling).
- **To prevent LV hypertrophy (remodeling) after acute MI through:**
  - ↓ arterial BP (↓ myocardial strain).
  - ↓ myocyte cell hypertrophy, apoptosis, and collagen synthesis.
- **Diabetic nephropathy & microalbuminuria:**
  - They ↓ renal changes complicating **diabetic nephropathy** (mesangial cell apoptosis, proliferation, and collagen synthesis), thus **reducing microalbuminuria** (provided that renal impairment is **not grave)**.

**Adverse effects:**

**C** : **Dry Cough** (the most common): inhibition of ACE leads to accumulation of bradykinin and PGs, which cause bronchial irritation and spasm.
Treatment: stop ACEIs. Cough will resolve after a few days.

**A** : **Angioedema** (edema of the face, tongue and throat): due to accumulation of bradykinin or due to immune reaction. It may be life threatening.

**P** : Aggravation of **Proteinuria** in patients with significant renal failure.

**T** : **Taste changes:** temporary loss of taste (ageusia and dysgeusia).

**O** : **Orthostatic (First dose) hypotension:** especially in sodium depleted (hypovolemic) patients.
Prevention: start by small at bedtime then increase gradually.

**P** : **Pregnancy:** teratogenesis (fetal pulmonary hypoplasia and renal dysfunction)

**R** : **skin Rash**

**I** : **Increased $K^+$ (hyperkalemia)** due to ↓ aldosterone release.

**L** : **Leukopenia** (neutropenia)**:** especially in patients with impaired renal function.

**N.B.** The sulfhydryl group (-SH) present in captopril may be responsible partially for the immunological side effects e.g. **angioedema, taste changes, skin rash, leukopenia.**

**Contraindications**

- **Hypotension:** when systolic BP is less than 95 mm Hg.
- **Severe renal failure or bilateral renal artery stenosis** (SCr > 3 mg/dl)**.** Why?
  - In these conditions, the use of ACEIs is dangerous because they ↓ Ang-II → ↓ VC of the efferent arterioles → ↓ glomerular filtration pressure and ↓ GFR → aggravation of renal failure in both kidneys.
  - Dangerous hyperkalemia may occur.
  - Dangerous neutropenia may occur.
- **Pregnancy and lactation:** they may cause fetal pulmonary hypoplasia and growth retardation.
- **Hyperkalemia.**
- **Neutropenia, thrombocytopenia**, or **severe anemia** (ACEIs may cause bone marrow depression).
- **Immune problems:** whether due to autoimmune diseases or due to immunosuppressive drugs.

**Precautions**

- Initial dose should be **small and at bedtime** to avoid 1st dose hypotension.
- Frequent monitoring of **kidney functions** (S. creatinine) and **potassium** levels one week after treatment and then every 3 months.
- Avoid use of **$K^+$ sparing diuretics** to avoid severe **hyperkalemia**.
- Remember all other contraindications…

## Angiotensin II receptor blockers (ARBs)
**(Losartan- Valsartan- Candesartan- Telmisartan)**

- They selectively block **$AT_1$** receptors and they exert most of the pharmacological effects seen with ACEIs.
- They have **no effect on bradykinin** metabolism.
- They have the potential for more complete inhibition of Ang-II action compared with ACE inhibitors because there are **non-ACE enzymes** (cathepsin and chymase) that can convert Ang-I into Ang-II.
- The **adverse effects and contraindications** are similar to those of ACE inhibitors but **cough** and **angioedema** are **less common** than with ACE inhibitors.

| | ACE inhibitors | ARBs |
|---|---|---|
| Class | Angiotensin converting enzyme inhibitor (ACEI) | Angiotensin receptor blocker (ARB) |
| Mechanism | Inhibition of ACE leading to: ↓ VC effect of Ang-II<br>↑ VD bradykinins | Blocking of AT-1 receptors leading to ↓ VC effect of Ang-II |
| Efficacy in inhibition of RAAS | Less effective because other enzymes rather than ACE can convert Ang-I into Ang-II | More effective because it blocks AT-1 receptor, the final station responsible for Ang-II effects. |
| Cough and angioedema | Frequent due to ↑ bradykinins | Less frequent (they do not ↑ bradykinins) |

## Direct renin inhibitors: aliskiren

- Activation of angiotensinogen into Ang-I by renin is the rate limiting step in formation of RAAS.
- Aliskiren is a recently approved drug for treatment of **hyperreninemic hypertension**. It inhibits renin activity and consequently the RAAS.
- The efficacy and side effects of aliskiren are comparable to ACEIs and ARBs.

## Calcium channel blockers (CCBs)

These are drugs that block **voltage-gated $Ca^{2+}$ channels.**

### Classification of CCBs according to tissue selectivity

- CCB with mainly **cardiac** effects: **verapamil, diltiazem.**
- CCB with mainly **vascular** effects (dihydropyridines): **nifedipine, amlodipine, nimodipine, nicardipine**
- CCB with main effect on **other tissue**: **flunarizine, cinnarizine**

### Types of $Ca^{2+}$ channels

**Voltage-dependent $Ca^{2+}$ channels**

They open in response to cell membrane depolarization

**L-type channels** (Long lasting):
- It is the dominant type in cardiac and vascular smooth ms.
- CCBs block this type of channels.

**T-type channels** (Transient).
**N-type channels** (Neuronal).

**Receptor operated $Ca^{2+}$ channels**

- These are $Ca^{2+}$ channels linked to G-protein receptors.
- They open in response to increase intracellular IP3.
- Examples: $Ca^{2+}$ channels coupled to α1 receptors.

### Pharmacological effects

| CVS | Nifedipine | Diltiazem | Verapamil |
|---|---|---|---|
| **Heart:** | | | |
| – Negative inotropic effect | — | ++ | +++ |
| – A-V conduction | — | ↓↓ | ↓↓↓ |
| – HR | ↑ (reflex) | ↓ | ↓↓ |
| **Blood vessels:** | | | |
| – Coronary VD | +++ | ++ | ++ |
| – Peripheral VD | +++ | ++ | ++ |
| – Blood pressure | ↓↓↓ | ↓ | ↓ |

### Other effects

- They **relax all smooth muscles** (vascular, bronchial, GIT, **uterine**, etc.).
- They ↓ $Ca^{2+}$- mediated **cell necrosis** and **apoptosis**.
- Verapamil ↓ **insulin release** from pancreatic beta cells but of little clinical significance.

### Therapeutic uses

#### Cardio-selective CCBs (verapamil & diltiazem):

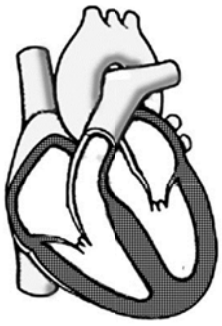
- **Ischemic heart disease (IHD):**
  - They ↓↓ myocardial contractility and myocardial $O_2$ demand.
  - They produce coronary VD and ↑ coronary blood flow.
  - They ↓ $Ca^{2+}$- mediated myocyte cell necrosis.

**N.B.** vasculoselective CCBs (dihydropyridines) e.g nifedipine are also beneficial in IHD but they cause considerable peripheral VD, so the dose should be adjusted to avoid hypotension and reflex tachycardia.

- **Cardiac arrhythmias: supraventricular tachycardia (SVT):**
  - SVT include atrial flutter, fibrillation, paroxysmal atrial tachycardia, etc.
  - Verapamil ↓ AV conduction, so it **protects** the ventricles from the rapid atrial rate (also β-blockers have the same effect).

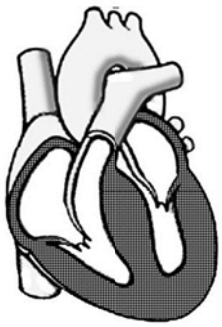
**N.B.** Nifedipine is contraindicated as it causes hypotension and reflex tachycardia.

- **Hypertrophic obstructive cardiomyopathy (HOCM):**
  - In hypertrophic obstructive cardiomyopathy, the wall of the left ventricle and interventricular septum is much thickened leading to narrowing of the aortic outlet and obstruction of blood flow.
  - Increasing contractility worsens the obstruction while decreasing contractility reduces resistance to blood flow through the aortic outlet and improve exercise tolerance.



Normal

**N.B.** Nifedipine is contraindicated because it produces reflex tachycardia → worsening of the outflow obstruction.



Hypertrophic cardiomyopathy

- **Arterial hypertension:**
  - They ↓ myocardial contractility and COP.
  - They cause peripheral VD due to ↓ $Ca^{2+}$ influx in the vascular smooth ms.

**Vasculo-selective CCBs (Nifedipine and amlodipine):**

- Arterial hypertension.
- Peripheral vascular disease (e.g. Raynaud's disease and intermittent claudication): to improve peripheral microcirculation.
- **Nifedipine** is sometimes used to relax the uterus and delay preterm labor.
- **Nimodipine** has high affinity for cerebral BV. It is used for prevention of cerebral vasospasm and ischemia complicating subarachnoid hemorrhage.

**Adverse effects**

**Verapamil & diltiazem:**

- Bradycardia and heart block.
- Worsening of CHF (due to their –ve inotropic effect).
- Constipation due to ↓ GIT motility.

**Nifedipine:**

- Hypotension and reflex tachycardia.
- Gingival (gum) hyperplasia.
- Salt & water retention (=ankle edema; more common than with verapamil due to significant VD and hypotension).

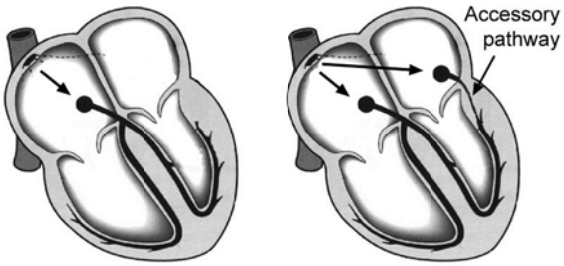
**How to treat ankle edema due to CCBs?**

- Minimize salt intake.
- Avoid prolonged standing.
- ACEIs.

**Contraindications & precautions**

**Verapamil & diltiazem:**

- Congestive heart failure.
- Bradycardia and heart block.
- Wolff-Pakinson-White syndrome:
  - In WPW syndrome, there is accessory conducting pathway between atria and ventricles other than the normal AV system causing a unique type of atrioventricular re-entry tachycardia.




  - As a rule, most drugs that ↓ AV nodal conduction (**A**denosine; **B**eta-blockers; **C**CBs; **D**igoxin) can paradoxically ↑ the conduction in the **abnormal** pathway leading to worsening of the tachycardia.
  - WPW syndrome can be managed by **amiodarone** but definitive treatment includes laser ablation of the accessory pathway (see later).
- Verapamil **should not** be combined with **digitalis** or **β-blockers** as it may aggravate bradycardia caused by these drugs *(nifedipine is the drug of choice to be used with β-blockers because it doesn't cause bradycardia).*

**Nifedipine:**

- Hypotension.
- Hypertrophic obstructive cardiomyopathy (HOCM) Why?
- Unstable angina (risk of reflex tachycardia).
- Supraventricular tachycardia (SVT) Why?

## Vasodilators

### Classification

- **Arterio-dilators: Nifedipine – Hydralazine – Minoxidil – Diazoxide**
  - They dilate arteries and ↓↓ BP (→ ↓ afterload)
  - They are used in severe systemic hypertension.
- **Venodilators: Nitrates**
  - They dilate mainly veins →↓ venous return (→ ↓ preload)
  - They are used in acute pulmonary edema.
- **Mixed dilators: Sodium nitroprusside – Prazosin – ACEIs – Trimetaphan**
  - They ↓ preload & afterload so they are used in CHF.

### General considerations

- Vasodilators relax vascular smooth ms and ↓ peripheral resistance.
- They usually cause **reflex sympathetic stimulation** (e.g. reflex tachycardia) so they can be combined with **beta-blockers**.
- They usually cause **salt and water retention** (due to reflex stimulation of aldosterone release) so they should be combined with **diuretics**.
- The use of vasodilators is **declining** as a result of newer modalities, such as ACEIs and CCBs, which are more effective with fewer adverse effects.

### Hydralazine

- It is a direct **arteriolodilator** by unclear mechanism.
- It is used in **severe hypertension** and hypertension in **pregnancy** (3rd choice after α-methyldopa and nifedipine).
- It is usually combined with **diuretics** to counteract salt and water retention, and **β-blockers** to counteract reflex tachycardia.
- It may cause **systemic lupus erythematosis** (SLE)-like syndrome especially in slow acetylators. The patient develops mild form of arthritis, renal impairment, and skin rash that usually disappear upon stopping of the drug.

SLE-like rash caused by hydralazine

### Minoxidil

- It is a direct **arteriolodilator** by **opening $K^+$ channels** → hyperpolarization → relaxation of the vascular smooth ms.

- It is given orally for **chronic hypertension** but its use as antihypertensive is declining; however, it should be combined with diuretics and β-blockers.
- It was found to stimulate **hair growth** (hypertrichosis) (by unclear mechanism), so it is now used **topically** to prevent hair loss in both males and females.

### Diazoxide

- Structurally related to **thiazides** but it is not diuretic
- It is a direct **arteriolodilator** by **opening $K^+$ channels** → hyperpolarization → relaxation of the vascular smooth ms.
- It is given parenterally in **hypertensive emergencies** but its use is declining.

### Sodium nitroprusside

- It liberates **nitric oxide (NO)** → ↑ cGMP → dilatation of both **arteries** and **veins** → ↓ both preload and afterload.
- It is given by **i.v. infusion** in **hypertensive emergencies** and **acute heart failure** because it has **rapid** action
- It can be converted to **cyanide** and **thiocyanate**. The accumulation of cyanide and risk of toxicity are minimized by concomitant administration of **sodium thiosulfate** (see angina) or **hydroxocobalamin** (vitamin B12).
- Sodium nitroprusside in aqueous solution is **sensitive to light** and must be made up **fresh** before each administration and covered with opaque foil.

### Fenoldopam

- It stimulates peripheral dopamine (**D1)** receptors in renal and mesenteric arteries, leading to VD and decrease peripheral resistance.
- It is used parenterally as a **rapid-acting vasodilator** to treat **emergency hypertension** in hospitalized patients.

## Endothelin-1 receptor antagonists

- **Endothelin-1** is 21 amino acid peptide. It is the predominant endothelin secreted by the vascular endothelium. It is elevated in patients with **pulmonary hypertension** and **coronary artery disease**.
- It acts on two types of receptors, **$ET_A$** and **$ET_B$**. $ET_A$ receptors is the main subtype in smooth ms and mediates **VC** and vascular smooth ms hypertrophy.
- **Bosentan** is orally active nonselective blocker of **$ET_A$** and **$ET_B$** receptors, while **ambrisentan** is a selective **$ET_A$** blocker.
- Both drugs are approved for treatment of **primary pulmonary hypertension**.

## Specialized vasodilators

**Drugs used for erectile dysfunction: Sildenafil, tadalafil**

- These drugs inhibit **phosphodiesterase (PDE) type 5** the enzyme responsible for breakdown of **cGMP** in erectile tissue (and lung) → ↑ cGMP → VD of the corpus cavernosum.
- They are very effective for treatment of **erectile dysfunction** in men. The effect of the drug appears after 30 min of oral administration and lasts for 4-5 hours.
- Sildenafil is also approved for treatment of **pulmonary hypertension**.
- **Side effects** include blue discloration of vision, headache, and optic neuropathy.
- These drugs are **contraindicated** in patients taking **nitrates** or **nicorandil** for treatment of angina because nitrates also act by ↑ cGMP leading to severe VD, hypotension, and reflex tachycardia → aggravation of angina and development of **arrhythmia**.

## Choice of the antihypertensive drugs:

| Clinical condition | Best choice |
|---|---|
| Starting therapy for non-complicated essential hypertension | Patient <55 years old: ACE inhibitors<br>Patient >55 years old: CCBs<br>If not adequate, add thiazide or beta blockers. |
| Hypertension of pregnancy | α-methyldopa<br>Labetalol – Nifedipine - Hydralazine |
| Hypertension in a diabetic patient with diabetic nephropathy (proteinuria) | ACE inhibitors |
| Hypertension with chronic kidney disease | S. creatinine <3 mg/dl: ACEIs<br>S. creatinine >3 mg/dl: CCBs |
| Hypertension with CHF | ACE inhibitors - diuretics |
| Hypertension with bronchial asthma | CCBs |
| Hypertension with angina | CCBs - beta-blockers |
| Hypertension with thyrotoxicosis, sympathetic overactivity, arrhythmia, or, HOCM | Beta-blockers |
| Hypertension with BPH | α1 blockers |
| Primary pulmonary hypertension | Endothelin receptor antagonists |

## Management of hypertensive emergencies:

**Hypertensive emergencies** are clinical situations associated with one or more of the following:

- BP > 180/120mmHg.
- Target organ damage e.g. cerebral stroke, encephalopathy, heart failure, aortic dissection, edema of the optic disc (papilledema).

Hypertensive encephalopathy

Is a clinical presentation consists of severe headache, mental confusion, blurred vision, and focal neurologic signs. If untreated it may progress over a period of 12–48 hours to convulsions, coma, and even death.

**Management:**

- Hospitalization and start parenteral therapy to lower BP rapidly (within a few hours not minutes).
- Chronic hypertension is associated with autoregulatory changes in cerebral, myocardial, and renal blood flow; so if sudden lowering of BP is done, cerebral, renal, and myocardial ischemic events can develop.
- The initial target in the first 1-2 hrs is to lower systolic BP by no more than **25%,** maintaining diastolic BP at no less than 100 mmHg.
- Drugs commonly used: **sodium nitroprusside**, **labetalol, fenoldopam,** all are given by slow **i.v.** infusion.
- Recent guidelines state that the following drugs are **not recommended**:
  - **Nifedipine**, **nitroglycerin**, and **hydralazine**: because these agents can cause sudden, uncontrolled, and severe reductions in BP that may precipitate cerebral, renal, and myocardial ischemic events with fatal outcomes.
  - **Furosemide** can lead to significant volume depletion and should be used only if there is associated volume overload as in case of pulmonary edema and acute heart failure.

## Part 2: Therapy of peripheral vascular disease (PVD)

It is a narrowing of the **arteries** other than coronary and cerebral vessels. It commonly affects arteries of lower limbs, but also renal and mesenteric arteries.

**Risk factors**

- Diabetes and smoking are the most important risk factors.
- Age > 65 years, hypercholesterolemia, hypertension and obesity.

**Manifestations**

- Intermittent claudication: pain in muscles when walking
- Rest pain in the soles of the feet, particularly when the feet are elevated.
- Skin: cool, bluish, ischemic ulcers.

**Management**

**Life-style:**

- Stop smoking: the most important factor
- Control of risk factors:
  - **Statins** for hypercholesterolemia.
  - Treatment of hypertension and DM.

An ischemic ulcer in a person with severe peripheral artery disease.

**Drug therapy:**

**Pentoxifylline**

- It increases RBC deformability by **inhibition of PDE enzyme**; this effect reduces blood viscosity and facilitates passage of RBCs through narrowed capillaries and ischemic sites.
- It is the 1st drug approved to improve microvascular circulation in patients with **intermittent claudication**, diabetic angiopathy, and chronic leg ulcers. Typical dose is 400 mg twice a day.

**Cilostazol**

- It is the 2nd drug recently approved for treatment of **intermittent claudication.**
- It inhibits **PDE enzyme (type 3)** leading to VD and ↓ platelet aggregation.
- **Headache** is the most common side effect.
- Cliostazol is **contraindicated** in patients with CHF because recent evidence showed that inhibitors of PDE enzyme type 3 increase mortality in those patients.

**Clopidogrel**

Antiplatelet agents such clopidogrel (75 mg/d) have additional benefits when compared with aspirin in diabetic patients with PVD.

# Part 3: Ischemic heart disease and antianginal drugs

## Basic information

### Ischemic heart disease includes:

- **Chronic stable angina (Classic; exertional angina):**
  - It is due to atheromatous narrowing of the coronary artery.
  - Pain is induced by effort and disappears with rest.

- **Acute coronary syndromes (ACS):**
  - ***Unstable angina:*** It is due to rupture of atheromatous plaque and formation of thrombus. The patient experiences acceleration in the frequency or severity of chest pain, or new-onset angina pain.
  - ***Myocardial infarction:*** An intraluminal thrombus completely occludes the epicardial coronary artery at the site of plaque rupture leading to irreversible coagulative necrosis.

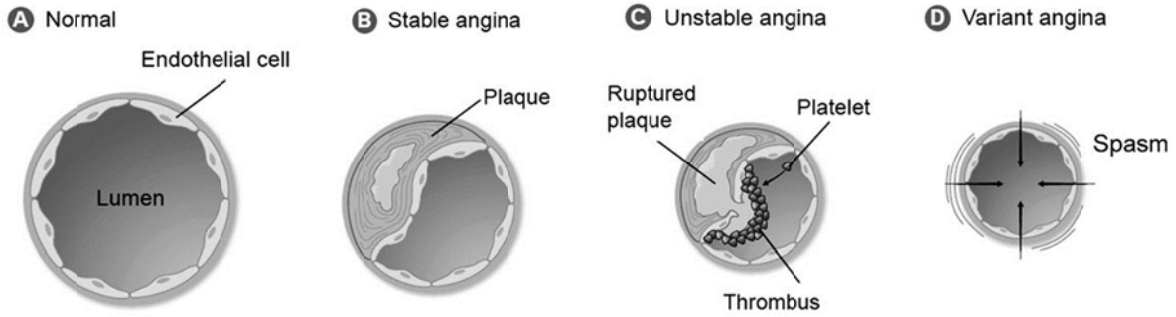
**Afterload:** it is the resistance that the ventricles must overcome to eject blood during systole. It is mainly determined by the resistance of the arterial side.

**Preload:** the stress (stretch) of the ventricular wall caused by venous filling just before contraction (also known as end-diastolic pressure). It is mainly determined by the amount of venous return (VR).

**N.B.** veins are capacitance vessels; venodilatation leads to decrease VR and preload.

- **Prinzmetal's angina (Variant angina; angina of rest; α-mediated angina):**

  The coronary artery undergoes severe spasm due to overactivity of $\alpha_1$ receptors. The patient develops pain at rest.




## Chronic stable angina

**Definition:** retrosternal pain due to ischemia of the myocardium as a result of imbalance between heart work *($O_2$ demand)* and coronary blood flow *($O_2$ supply)*.

**Clinical picture:**

**Central chest pain** is the cardinal symptom:

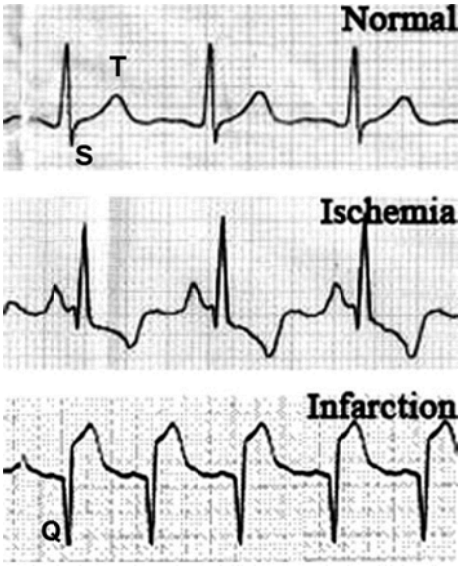
- Site and radiation: retrosternal, radiating to the left shoulder and the left arm.
- Character: any character *(usually sense of chest tightness)*.
- Precipitated by 3E: **e**xertion, **e**motion, **e**ating, and relieved by rest and nitrates.
- Duration: usually < 10-15 min. If longer than 15 min → suspect ACS.

**Diagnosis:**

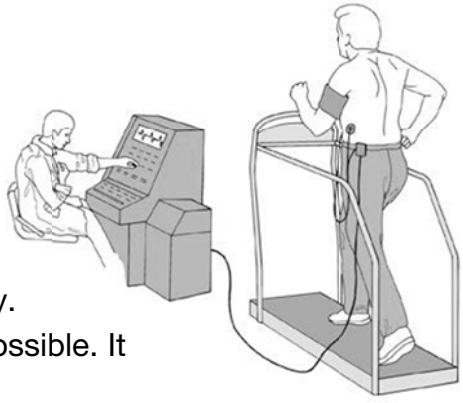
- **ECG:**
  - Resting 12-lead ECG: this is often normal *and does not exclude ischemic heart disease.*
  - During attack: there is ST segment depression and T-wave inversion.
  - In myocardial infarction: ST elevation and deep Q-wave.
- **Exercise ECG:** recording ECG under controlled physical effort to record ischemic changes.
- **Nuclear isotope stress imaging.**
- **Coronary angiography.**

**Guidlines**

- Do not use people's response to glyceryl trinitrate (GTN) to make a diagnosis.
- Refer people to hospital as an emergency if an ACS is suspected.
- Do not exclude an ACS when people have a normal resting 12-lead ECG.
- Do not routinely administer oxygen. Only offer oxygen to:
  - People with arterial oxygen saturation (SaO2) < 92%.
  - People with COPD.




## Management of stable angina



- **Non-drug therapy = life style modification:**
  - The same as hypertension (see before).
- **Pharmacological therapy:**
  - **Immediate treatment of acute chest pain:**
    - Glyceryl trinitrate (GTN): sublingual or spray.
    - Aspirin 300 mg loading dose as soon as possible. It reduces the risk of progression to MI.
    - Refer the patient to hospital if an ACS is suspected.
  - **Long-term therapy:**

- Beta-blockers: the first-line agents for chronic stable (exertional) angina.
- CCBs: the second-line agents for chronic stable angina
- Long and intermediate acting nitrates.
- pFOX inhibitors: trimetazidine
- Newer antianginal drugs: ranolazine and nicorandil
- Lipid lowering drugs: statins (see chapter 6).
- Antiplatelet drugs: e.g. aspirin, clopidogrel (see pharmacology of blood).

- **Surgical treatment (myocardial revascularization).**

## Organic nitrates and nitrites

### Classification

| | Dose | Onset | Duration |
|---|---|---|---|
| **Short-acting nitrates:** | | | |
| Amyl nitrite crushable ampoules | 0.3 ml inhalation | 1-2 min | 5-10 min |
| Glyceryl trinitrate tablets or spray | 0.5 mg SL | 1-5 min | 10-20 min |
| Isosorbide dinitrate | 5 mg SL | 3-5 min | 60 min |
| Glyceryl trinitrate (Tridil®) | 5 µg/min i.v.i. | | |
| **Intermediate-acting nitrates:** | | | |
| Isosorbide dinitrate | 10 mg oral | 15 min | 3-6 hrs |
| | 40 mg oral SR | 30 min | 6-10 hrs |
| **Long-acting nitrates:** | | | |
| Isosorbide mononitrate | 20 mg oral | 30 min | 6-8 hrs |
| | 60 mg oral SR | 30 min | 6-10 hrs |
| **Transdermal patches** | | 30 min | 12-18 hrs |

### Pharmacokinetics

**Absorption:** nitrates are rapidly absorbed from all sites of administration.
**Metabolism:** in the liver:

- If given oral → **extensive first-pass** metabolism (oral bioavailability <10%)
- If given sublingual → **no first-pass** metabolism → high bioavailability.
- Mononitrate: has **no hepatic metabolism** → long duration of action.

**Excretion:** via the kidney.

### Mechanism of action

- Nitrates cause formation of the free radical **nitric oxide (NO)** which is identical to the endothelial derived relaxing factor **(EDRF)** → ↑ cGMP → VD (more on veins than arteries).
- They also ↑ formation of vasodilator PGE2 and $PGI_2$.

**Pharmacological effects**

**CVS:** Blood vessels:

- VD of the venous (and to lesser extent the arterial) side leading to ↓ preload and ↓ afterload → ↓ cardiac work.
- VD of coronary arteries leading to increased coronary blood flow.
- VD of arteries in the face and neck leading to *flushing of the face.*
- VD of meningeal arteries leading to *throbbing headache*.

Heart: Reflex tachycardia (in high dose) 2ry to ↓ BP.
BP: High doses cause ↓↓ in both systolic and diastolic BP.

**Smooth ms:** Relaxation of all smooth ms (bronchial, GIT, uterine, and biliary).

**Respiration:** Reflex tachypnea due to hypotension in **high** doses.

**Blood:** Methemoglobinemia in **high** doses due to oxidation of Hb into met-Hb.

**Therapeutic uses**

- **Angina pectoris**

  Nitrates are used for treatment of all types of angina both for relieving the **acute** attack and for prophylaxis. The **mechanism** is due to:

  - Nitrates cause formation of the free radical **nitric oxide (NO)** which is identical to the endothelial derived relaxing factor **(EDRF)** → ↑ cGMP → VD (more on veins).
  - They also ↑ formation of vasodilator $PGE_2$ and $PGI_2$.

  **These effects lead to:**

  - Decrease cardiac work & myocardial $O_2$ demand through:
    - Venodilatation → ↓ venous return (preload = ↓ end-diastolic pressure).
    - Arteriolodilatation → ↓ peripheral resistance (afterload).
  - Enhancement of coronary blood flow (perfusion) through:
    - Coronary VD.
    - Redistribution of blood from large epicordial vessels to ischemic subendocardial vessels.

- **Myocardial infarction:** to ↓ the area of myocardial damage.
- **Acute heart failure:** to ↓ preload and afterload.
- **Treatment of cyanide poisoning:** see box

### Adverse effects

- **Hypotension** and **reflex tachycardia:** may aggravate angina.
- **Throbbing headache:** due to VD of meningeal arteries.
- **Flushing** of the face.
- **Nitrate tolerance:** means diminished response to nitrates with continuous administration which cannot be corrected by increasing the dose. The exact mechanism is unclear but there are 2 theories to explain this:
  - Recent studies showed that continuous administration of nitrates leads to formation of **free radicals** of the reactive oxygen species (ROS) leading to oxidation and inhibition of the enzyme MALDH2 responsible for bioactivation of nitrites into the vasoactive NO.
  - Prolonged VD by nitrates leads to reflex sympathetic stimulation and activation of renin-angiotensin system → VC and salt & water retention.
  - Prevention of nitrate tolerance: make a daily **nitrate-free interval** (10–12 h) to give chance for bioactivating enzymes to regenerate. During this period, give another anti-anginal drug e.g. beta-blocker or CCBs.
- **Methemoglobinemia:** rare and require high doses.

**Treatment of cyanide poisoning**

**Principle:** cyanide has high affinity for metHb more than normal Hb.

- **Sodium nitrite** (300 mg i.v.) is given to convert part of Hb to metHb to attract cyanide ions and form cyan-metHb.
- **Sodium thiosulphate** (25 gm i.v.) is given to convert cyan-metHb to thiocyanate (non-toxic) → renal excretion.

### Precautions during nitrate therapy

- Use the **smallest effective dose** to avoid hypotension and reflex tachycardia.
- The patient should **consult his doctor** if anginal pain does not improve after taking 3 SL tablets of GTN during 15 min (the pain may be due to MI).
- Nitroglycerine tablets should not be put in **direct sunlight** (light sensitive) or with **cotton** (to avoid formation of the explosive *nitrocellulose*).
- The **expiry date** should be checked (active tablets have **burning** taste).
- Nitrates should not be used with **sildenafil.** Why?

## Beta-blockers

- Beta-blockers are considered first-line in **chronic exertional** (classic) angina *(note that short acting nitrates are the first line during the **acute** attack)*.
- Treatment objectives include lowering the resting HR to 50-60 beats/min and limiting maximal exercise HR to ~ 100 beats/min or less.

- There is little evidence to suggest superiority of any particular β-blocker, but β-blockers with ISA should be avoided because the reduction in HR and O2 consumption would be minimal.
- They are contraindicated in **Prinzmetal's (variant) angina** because they block the $\beta_2$-mediated coronary dilatation leaving the $\alpha_1$ receptors unopposed → ↑ coronary spasm.

**Mechanism of β-blockers in exertional angina**

- They ↓ contractility, HR, and systolic BP → ↓ myocardial work and $O_2$ demand.
- They ↑ diastolic (coronary) filling time.
- Cause redistribution of blood from normal to ischemic (subendocardial) regions
- Cytoprotective effect: they produce metabolic switch from myocardial *fat* utilization to *carbohydrates* utilization (i.e. improves myocardial metabolism).

**Combination of BBs and nitrates** ↑ their efficiency & ↓ their side effects**:**

| | β-blockers | Nitrates | Combination |
|---|---|---|---|
| – **HR** | ↓ | ↑ (Reflex) | ↓ or no effect |
| – **Contractility** | ↓ | ↑ (Reflex) | ↓ or no effect |
| – **Diastolic filling time** | ↑ | ↓ | ↑ or no effect |
| – **Blood pressure** | ↓ | ↓ | ↓↓ |

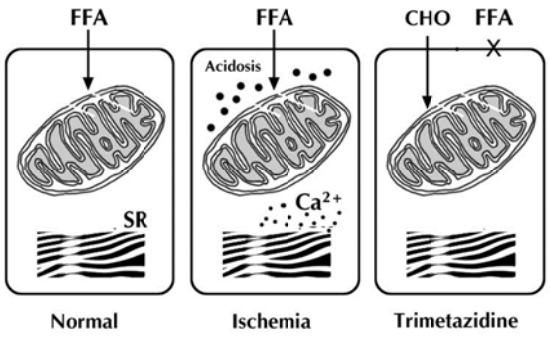
## Calcium channel blockers (CCBs)

- They are considered first-line treatment for **Prinzmetal's** (variant) angina.
- They are considered second-line alternative after beta-blockers in chronic stable angina in whom beta-blockers are contraindicated.
- Short acting dihydropyridines are associated with increased risk of ACS and should be avoided. Long acting dihydropyridines (e.g. amlodipine) and non-dihydropyridines (verapamil and diltiazem) are more preferred.
- **Amlodipine** is the CCB of best choice for symptomatic treatment of angina and/or hypertension in patients with chronic heart failure.

## Newer options for treatment of chronic angina

- **pFOX inhibitors, potassium channel openers,** and **ranolazine** are examples of new anti-anginal drugs. These drugs alter the balance between myocardial work and O2 supply by novel mechanism(s) of action.
- Their efficacy in treatment of angina is controversial; however they are approved for treatment of chronic stable angina **in combination** with β-blockers, CCBs, and nitrates.

**pFOX inhibitors (metabolic modifiers): Trimetazidine**




- They are termed pFOX inhibitors because they partially **inhibit fatty acid oxidation** in the myocardium.
- This "metabolic switch" from fats to carbohydrate utilization requires less $O_2$ consumption.
- By inhibition of fatty acid oxidation, they ↓ intracellular lactic acidosis leading to ↓ intracellular $Ca^{2+}$ & $Na^{+}$ accumulation and ion disturbance, so they prevent cell necrosis and preserve contractile function.
- It does not affect HR, blood pressure or coronary blood flow.

**Potassium channel openers: Nicorandil**

- Nicorandil is a new antianginal drug with 2 proposed mechanisms of action:
  - It opens ATP-dependent $K^{+}$ channels in the vascular wall leading to VD of peripheral and coronary arteries.
  - Nitrate-like activity: it has a nitrate component and ↑ cGMP like nitrates but tolerance to its effects is less marked.
- Like nitrates, it should **not** be used with **sildenafil**.

**Ranolazine**

- It ↓ intracellular $Ca^{2+}$ indirectly by reducing the late $Na^{+}$ current that facilitates $Ca^{2+}$ entry into myocardial cells. The reduction in intracellular $Na^{+}$ and $Ca^{2+}$ load reduces cardiac contractility and work.
- It does not affect HR, blood pressure or coronary blood flow.

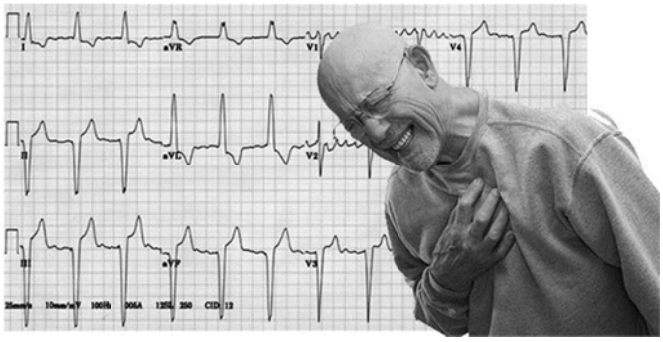
**Antiplatelets and cholesterol lowering drugs:** see pharmacology of blood.

**Choice of antianginal drugs in patients with another disease:**

| Angina with…. | Most preferred | Least preferred |
|---|---|---|
| Bronchial asthma | Nitrates, CCBs | Beta-blockers |
| Heart failure | Amlodipine | Beta-blockers, Verapamil |
| Hypertension | Beta-blockers, CCBs | Nitrates |
| Diabetes mellitus | Nitrates, Nifedipine | Beta-blockers, Verapamil |

## MANAGEMENT OF ACUTE MYOCARDIAL INFARCTION (AMI)

**Manifestations:** persistent central crushing chest pain + ST segment elevation or depression + pathological Q wave + raised biochemical markers of myocardial cell death (troponin enzyme).
All cases must be **hospitalized** in a specialized coronary care unit.



### ■ Non-pharmacologic therapy:

Patients presenting within 12 hours of symptom onset, the treatment of choice is percutaneous coronary intervention (PCI, or coronary angioplasty). A balloon catheter, guided by x-ray imaging, is introduced into the occluded artery to open it.

### ■ Pharmacologic therapy:

- **Morphine sulfate (5 mg i.v.):**
  - To produce analgesia and ↓ stress of the patient → ↓ sympathetic discharge and heart work.
  - Morphine causes venodilatation → ↓ venous return and cardiac work.
- **Oxygen:** recent evidence suggests that routine O2 administration has doubtful significance and did not reduce mortality.
- **Nitroglycerine** and **beta-blockers:** to limit the infarct size.
- **Anticoagulant drugs: heparin** 10,000 IU i.v. then 5000 IU/8h s.c. especially when the patient is obese or if there is history of previous MI.
- **Thrombolytic (fibrinolytic) therapy:** streptokinase, urokinase, or t-PA as early as possible (see blood).
- **Sedatives:** diazepam 5 mg i.v.
- **Treatment of Complications:**
  - Cardiogenic shock → dobutamine i.v.i - Arrhythmia → lidocaine i.v.

**Morphine and AMI**

Morphine is usually given s.c. but in AMI it is given **5 mg i.v.**

Morphine is contraindicated in cases of MI involving the inferior wall of the heart **(inferior MI)** because in this case, the patient has bradycardia and morphine causes **vagal stimulation** and aggravates bradycardia.

**Meperidine** is a good alternat-ive in cases of inferior MI because it has **atropine-like action** and counteract bradycardia.

**What other opioid analgesics are contraindicated in AMI?**

**Pentazocin** and **butorphanol** because they *increase pulmonary and systemic vascular resistance with more strain on the heart* (see CNS).

# Part 4: Therapy of congestive heart failure (CHF)

## Basic information

**Definition:** Heart failure (HF) is a progressive **clinical syndrome** in which either structural or functional abnormalities impair the ability of the heart to meet the metabolic demands of the body. .

**Classification, clinical picture, and therapeutic aim:**

- **Anatomical classification**

**Left-sided heart failure (LSHF):**
- Usually due to systemic hypertension.
- The cardinal manifestations are those of **pulmonary congestion** e.g. tachypnea, dyspnea (difficulty in breathing), orthopnea (dyspnea on lying back), paroxysmal nocturnal dyspnea, cough with expectorations, bilateral basal lung crepitation, etc.

**Right-sided heart failure (RSHF):**
- Usually due to pulmonary hypertension or lung disease.
- The cardinal manifestations are those of **systemic congestion** e.g. congested neck veins, congested liver, bilateral leg edema, right ventricular hypertrophy, etc.

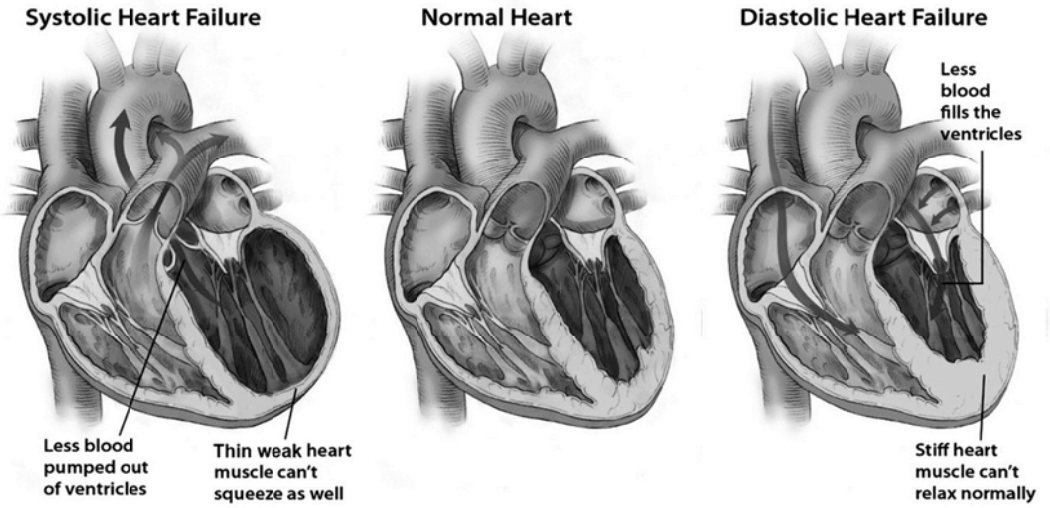
**Total or congestive heart failure (CHF):** combination between the two.

- **Pathological classification**

**Systolic dysfunction (decreased contractility)** is caused by reduced muscle power e.g, MI, cardiomyopathies, and ventricular hypertrophy (strain). Ventricular hypertrophy can be caused by *pressure overload* (e.g, systemic or pulmonary hypertension and aortic or pulmonic valve stenosis) or *volume overload* (e.g, valvular regurgitation, high-output states e.g. thyrotoxicosis and arteriovenous fistula).

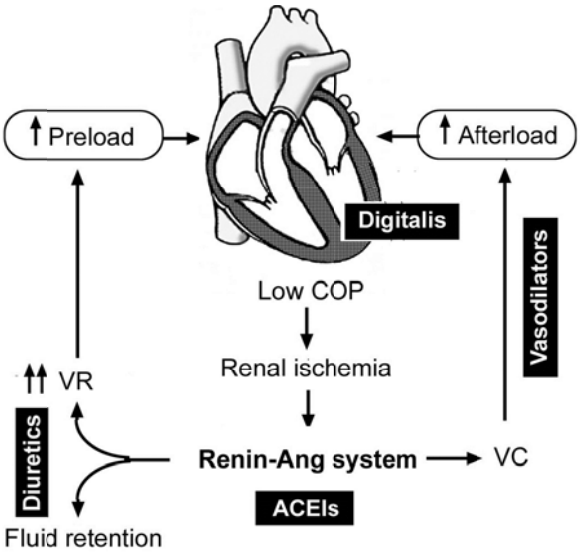
**Diastolic dysfunction (restriction in ventricular filling)** is caused by increased ventricular stiffness e.g. ventricular hypertrophy, infiltrative myocardial diseases

(e.g. amyloidosis), myocardial ischemia and MI, and pericardial disease (e.g, pericarditis and fibrosis).


Systolic Heart Failure
Normal Heart
Diastolic Heart Failure
Less blood fills the ventricles
Less blood pumped out of ventricles
Thin weak heart muscle can't squeeze as well
Stiff heart muscle can't relax normally

**The decreased COP leads to the following compensatory mechanisms:**

- Sympathetic overactivity leading to tachycardia.
- Renal ischemia → ++ of RAAS → VC (Ang-II) and fluid retention (aldosterone) → ↑ afterload and preload → more HF and edema (vicious circle).




## ■ Clinical classification

HF is classified by the New York Heart Association (NYHA) into the following classes:

| NYHA Class | Symptom |
|---|---|
| I (mild) | No symptoms while performing ordinary physical activity (walking, climbing stairs, etc.). |
| II (mild) | Mild symptoms (mild shortness of breath, palpitations, fatigue, and/or angina) and slight limitation during ordinary physical activity. |
| III (moderate) | Marked limitation in activity due to symptoms, even during less than ordinary activity. Comfortable only at rest. |
| IV (severe) | Severe limitations with symptoms even while at rest. Mostly bedbound patients. |

## Therapy of heart failure

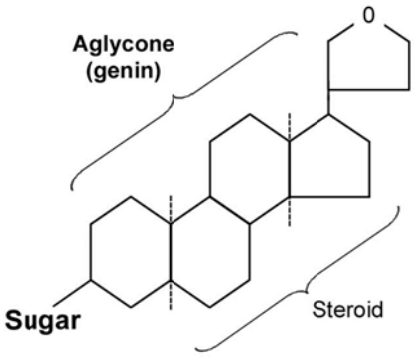
- **Non-drug therapy = life style modification:**
  - Rest.
  - Dietary **s**odium (salt) and fat restriction.
  - Avoid **s**tress, **s**moking and alcohol.
  - Weight reduction.
  - Control of risk factors e.g. surgical correction of valvu**l**ar diseases and treatment of hyperthyroidism, hypertension, etc.
  - Avoid drugs that ↑ BP: e.g. sympathomimetics, sodium containing drugs, etc.

- **Drug therapy:**
  - Positive inotropic drugs:
    - Cardiac glycosides (Digitalis).
    - Dopamine & dobutamine (used for **short term** only).
    - Phosphodiesterase inhibitors: inamrinone & milrinone.
  - Diuretics.
  - ACEIs.
  - Vasodilators: nitrates and hydralazine
  - Other drugs: e.g. beta-blockers and spironolactone.

## Cardiac glycosides:

**Digoxin, Digitoxin, Ouabain**

### Source and chemistry




- Natural plant derivatives (Foxglove plant).
- Cardiac glycosides contain a lactone ring and a steroid (aglycone) moiety attached to sugar molecules.
- Digoxin is the most widely used.

### Pharmacokinetics of digoxin

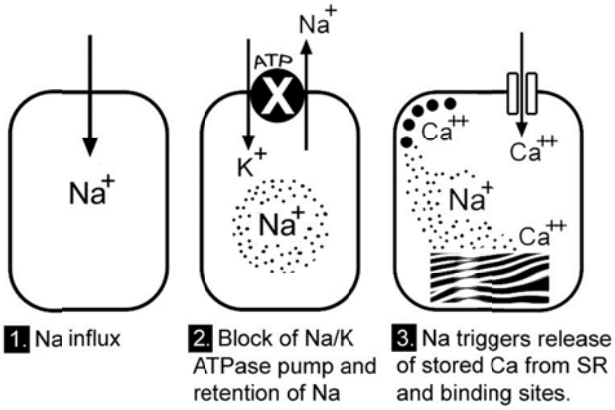
- Digoxin distributes to most body tissues and **accumulates in cardiac tissue**. The concentration of the drug in the heart is twice that in skeletal muscle and at least 15 times that in plasma.
- Elimination is **renal**. Dose adjustment should be done according to **creatinine clearance**.

### Mechanism of action

- **Positive inotropic effect:**

Digitalis ↑ cardiac contractility by increasing free intracellular $Ca^{2+}$ through **inhibition of membrane-bound $Na^+/K^+$ ATPase enzyme**. This result in inhibition of $Na^+/K^+$ pump with subsequent accumulation of intracellular $Na^+$ and $Ca^{2+}$ via:

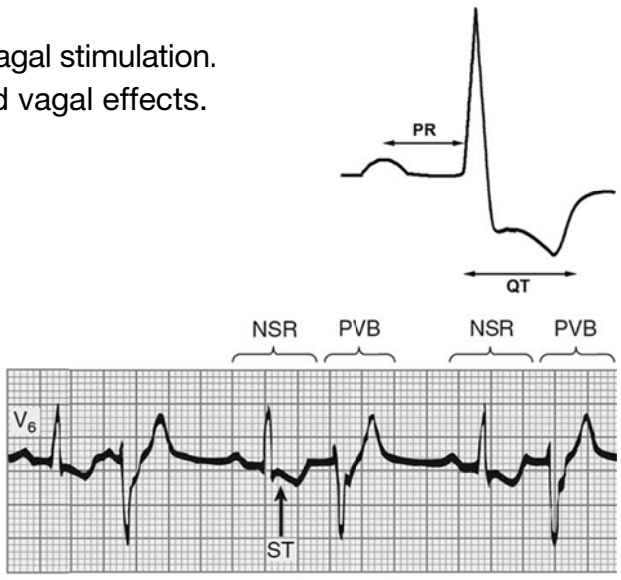
- Increase $Ca^{2+}$ release from the sarcoplasmic reticulum.
- Displacement of intracellular $Ca^{2+}$ from its binding sites.
- Increased intracellular $Na^+$ prevents $Ca^{2+}$ expulsion from the cell by the $Na^+/Ca^{2+}$ exchanger.




- **Autonomic effects:**
  - ↑ vagal activity: By direct and indirect mechanisms.
  - ↓ sympathetic activity due to relieve of hypoxia & improved tissue oxygenation.

**Pharmacological effects**

- ↑ **Contractility and COP:** due to +ve inotropic effect. This leads to:
  - Improvement of RBF → **diuresis** and ↓ RAAS (i.e. ↓ fluid retention).
  - Relief of lung congestion.
- ↓ **HR: (B r a d y c a r d i a )** due to:
  - ↑ vagal tone and ↓ sympathetic activity on the heart.
  - Direct inhibition of the AV conducting system.
- **Conduction velocity:**
  - Intra atrial conduction: ↑ due to vagal stimulation.
  - A-V conduction: ↓↓ by direct and vagal effects.
- ↑ **Excitability and automaticity:** leading to ectopic foci and arrhythmia of any type (bigeminy, trigeminy, etc.).
- **ECG changes:**
  - Prolonged PR interval.
  - Short QT interval.
  - ST segment depression & T-wave inversion.
- **Normalization of arterial and venous pressures** due to improved hemodynamics.




ECG record showing digitalis- induced bigeminy. The complexes marked NSR are normal sinus rhythm beats; an inverted T wave and depressed ST segment are present. The complexes marked PVB are premature ventricular beats

### Therapeutic indications

- The use of digoxin is now limited to cases of **chronic CHF associated with atrial flutter or fibrillation (AF)** because digoxin is the only drug that ↑ contractility and ↓ AV conduction in the same time.
- In cases of AF alone, other drugs like verapamil or beta-blockers are preferred.
- In cases of CHF without AF, other drugs like diuretics and ACEIs are preferred.

### Contraindications

- **Absolute contraindications:**
  - **Heart block:** because digitalis worsens AV conduction by direct and vagal effects.
  - **Hypertrophic obstructive cardiomyopathy (HOCM):** because increasing cardiac contractility will ↑ the outflow tract resistance and accelerates heart failure (see before).
  - **Wolff-Parkinson-White (WPW) syndrome:** although digitalis (and verapamil) ↓ conduction in the normal pathway, they can ↑ conduction in the **abnormal** pathway leading to ↑ arrhythmia (see before).
  - **Paroxysmal ventricular tachycardia:** digitalis ↑ excitability and automaticity.
- **Relative contraindications:**
  - All causes of **bradycardia** (e.g. sick sinus syndrome, hypersensitive carotid sinus, with beta-blockers or verapamil) because addition of digoxin can lead to severe bradyvardia or even heart block.
  - **Systemic hypertension:** digitalis will ↑ the strain of the LV (you must correct hypertension first by giving VDs or diuretics).
  - **Pulmonary hypertension** due to **chronic lung disease:** digitalis will ↑ the strain of the RV (you must correct pulmonary hypertension first by giving VDs).
  - **Cardiac diseases:**
    - Acute MI: digitalis ↑ the infarct size and aggravates arrhythmia.
    - Cardiomyopathy…. digitalis is useless.
  - **Renal or hepatic diseases:** digoxin must be avoided in renal patients while digi**T**oxin must be avoided in hepa**T**ic patients.
  - In patients likely to require **cardioversion:** because digitalis may lead to fatal arrhythmia if given with cardioversion.

**Drug interactions**

| Drug | Mechanism/effect |
|---|---|
| **Antacids - Kaolin Cholestyramine** | Bind digoxin in the gut and decrease bioavailability (absorption) |
| **Metoclopramide** | Increase gut motility leads to decrease digoxin absorption. |
| **Atropine** | Decrease gut motility leads to increase digoxin absorption |
| **Quinidine** | Decrease renal clearance of digoxin and displace digoxin from plasma proteins. Serum digoxin is increased. |
| **Loop diuretics and thiazides** | Thiazides or loop diuretics may cause **hypokalemia** and hypomagnesemia which can ↑ the risk of digitalis **toxicity** |

**Dosage and administration**

- **Initial digitalization:**
  - It is done by giving **one tablet** 0.25 mg /day (5 days/week) from the start.
  - The Cpss will be achieved after **5 t½** (i.e. after one week for digoxin).
  - **Rapid (loading) method** is done in emergency conditions to achieve rapid Cpss. It is given as **2 tablets** (0.5 mg) **twice** daily for **2 days (2x2x2).**
- **Maintenance dose:** one tablet (0.25 mg)/day, 5 days/week.

**N.B.**

- The optimum therapeutic plasma level is **1–2 ng/ml.**
- Arrhythmia occurs when the level exceeds **2 ng/ml.**

**Assessment of response to digitalis**

- Relief of dyspnea and orthopnea.
- Relief of tachycardia and tachypnea.
- Relief of edema, lung congestion, and fatigue.
- Increase urine volume. Improvement of physical performance.

**Precautions during digitalis therapy**

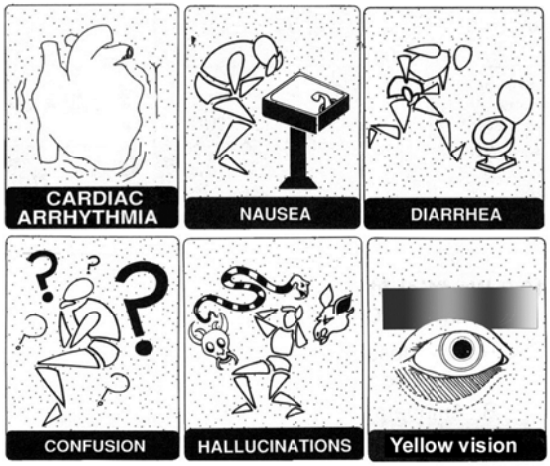
- Never give digitalis i.v. before being sure that the patient has not received digitalis during the last 14 days to avoid digitalis toxicity.
- Continuous monitoring of plasma $K^+$ level.
- Mention all the **relative contraindications.**

## Digitalis toxicity

**Predisposing factors**

- **Hypokalemia:** increases digoxin binding and effect.
- **Hypercalcemia** (N.B. Hypocalcemia renders digitalis less effective).
- Presence of renal impairment.

**Manifestations**




- **Cardiac:**
  - Bradycardia and variable degree of heart block.
  - Paroxysmal atrial tachycardia
  - Any type of arrhythmia (premature beats, bigemeny, trigemeny, etc.)

- **Extracardiac:**
  - The **first** manifestation is **fatigue** and **anorexia**, followed by GIT symptoms e.g. diarrhea, nausea & vomiting due to stimulation of CTZ.
  - CNS: headache, delirium, hallucination, and convulsions.
  - Vision: **yellow vision** (chromatopsia), diplopia, amblyopia, scotoma, etc. due to retrobulbar neuritis.
  - Others: skin rash, gynecomastia, galactorrhea.

**Management**

- Stop digitalis administration.
- Correct hypokalemia by giving $K^+$ either i.v. or oral (2 gm/4 h).
- Antiarrhythmic drugs:
  - Lidocaine (in ventricular arrhythmia): 1-2 mg/kg i.v. bolus then 1-2 mg /min i.v.i.
  - Phenytoin (in ventricular arrhythmia with heart block): 250 mg i.v. over 10 min.
  - Atropine: if there is bradycardia or heart block.
- Specific digitalis antibodies **(Fab fragments; Digibind)** to bind digitalis and promote its renal clearance (the most **specific** therapy).

## Other positive inotropic drugs

### Phosphodiesterase (PDE) inhibitors: Inamrinone – Milrinone

- They inhibit PDE enzyme (type **3**) → ↑ cAMP → ↑ $Ca^{2+}$ influx in myocardial cells → ↑ myocardial contractility.
- They have VD properties.
- They are used only **i.v.** for **short term** treatment of **CHF** in patients not responding to digitalis. They are not safe for long term use.
- **Adverse effects include:** thrombocytopenia, cardiac arrhythmia, increase liver enzymes (hepatotoxicity).
- Milrinone is less toxic than inamrinone

## Diuretics

### Mechanism in heart failure

- They ↓ fluid retention and pulmonary congestion leading to improvement of tissue oxygenation
- They ↓ preload & afterload so improve myocardial function.
- **Spironolactone** antagonizes the effect of aldosterone that is increased in CHF due to secondary stimulation of RAS. Recent evidence showed that it reduces mortality rates in patients with advanced heart failure (NYHA class III and IV).

### Disadvantages of diuretics

- Excessive use of diuretics will ↓ ECF volume → ↓ COP.
- Diuretic-induced acid-base imbalance may impair cardiac function.
- Diuretic-induced hypokalemia can ↑ digitalis toxicity and cardiac arrhythmia.

These adverse effects could be minimized by **diuretic combination** (loop diuretics plus $K^+$ sparing diuretics) to minimize hypokalemia and acid-base imbalance.

## Vasodilators (nitrates and hydralazine)

- **Nitrates** and **hydralazine** have complementary hemodynamic actions:
  - Nitrates are primarily venodilators, →↓ preload.
  - Hydralazine is a direct arterial dilator →↓ systemic vascular resistance and afterload.
- Recent evidence showed that combination of nitrates and hydralazine reduces mortality and hospitalizations for patients with HF.
- A fixed-dose combination product is available (USA and Europe) that contains isosorbide dintrate 20 mg and hydralazine 37.5 mg.
- Guidelines recommend addition of hydralazine and nitrates to moderate to severe HF despite therapy with ACE inhibitors, diuretics, and β-blockers.
- The combination is also appropriate as first-line therapy in patients unable to tolerate ACE inhibitors or ARBs due to any contraindication.

## ACEIs and ARBs

### Beneficial effects in heart failure:

- They ↓ arterial BP → ↓ afterload.
- They ↓ aldosterone → ↓ Na & $H_2O$ retention → ↓ preload.
- They prevent myocardial wall thickening and cardiac remodeling.

## Beta-blockers

High doses of β-blockers are generally not recommended in heart failure because they produce –ve inotropic effect and may precipitate cardiac decompensation, but **small doses** have some benefits in heart failure:

According to recent evidence, a number of drugs have been shown to reduce mortality in patients with chronic HF. These are:

- **ACE inhibitors**
- **Spironolactone**
- **Beta-blockers**
- **Hydralazine with nitrates**

**Beneficial effects in heart failure:**

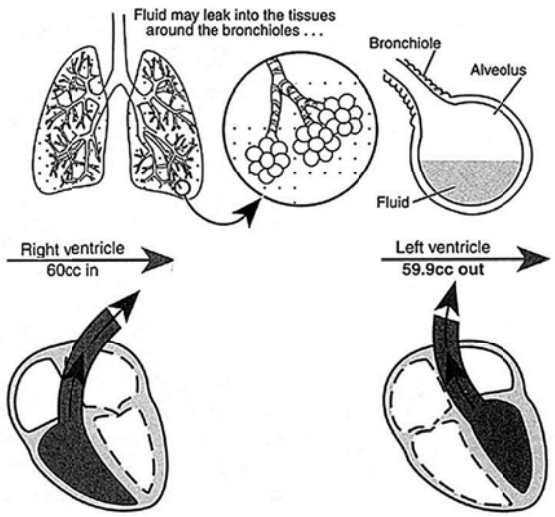
- β-blockers reduce tachycardia and sympathetic overactivity.
- β-blockers reduce BP → ↓ ventricular strain associated with HF.
- β-blockers inhibit renin release → ↓ cardiac remodeling caused by RAAS.
- **Carvedilol** is a new beta-blocker with additional VD and antioxidant properties.

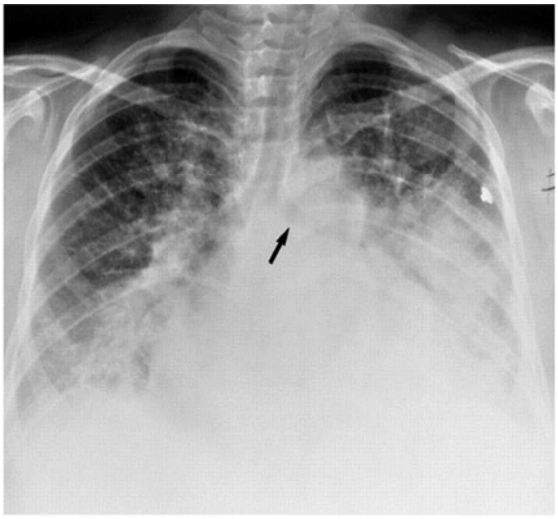
According to currently available evidence, **bisoprolol, metoprolol,** and **carvedilol** have shown the most useful effects in patients with chronic HF.

## MANAGEMENT OF ACUTE CARDIOGENIC PULMONARY EDEMA

### Pathophysiology of APE

Acute cardiogenic pulmonary edema (APE) is accumulation of fluid (transudate) in the lung interstitium and alveoli as a result of increased capillary hydrostatic pressure secondary to LV dysfunction.



### Manifestations

– Dyspnea, orthopnea and wheezes.
– **Chest x-ray**: patchy or diffuse alveolar filling (haziness).

**Management**

- Hospitalization and **sitting** or semi-sitting position.
- High-flow **oxygen** *(hypoxia causes pulmonary VC and increased cardiac load).*
- **Furosemide** (20-80 mg IV): to ↓ venous return and pulmonary congestion. It is the most important treatment.
- **Morphine** (2-4 mg IV):
  - To ↓ stress and anxiety.
  - Venodilatation → ↓ VR → ↓ lung congestion.
  - It ↓ pulmonary stretch reflex → ↓ tachypnea & work of breathing.
- **Nitroglycerine** (sublingual or i.v.).
- Hemodynamic support according to systolic BP:
  - Maintain systolic BP >100 mmHg.
  - If the SBP is <100 mmHg, start IV **dopamine** or **dobutamine** at 5-15 µg/min.

**N.B.**
Digoxin is indicated only if rapid AF is present.

## Part 5: Management of shock

**Shock** is a circulatory disorder. It is complex state of hypotension and impaired tissues perfusion of vital organs (acute circulatory failure).

**Diagnosis**

- Systolic BP **< 90** mmHg OR mean arterial BP (MAP) **< 60** mmHg.
- Tachycardia and tachypnea
- Oliguria (urine < 20 ml/h), or anuria.
- Cool pale extremities with slow capillary refilling.
- Confusion and restlessness.

### Anaphylactic shock

It is a medical emergency that requires immediate recognition and intervention.

**Causes, manifestations, and time course**

Acute hypersensitivity reaction in response to allergic substance (food, drugs or venom) → massive release of histamine from mast cells:

  - Skin changes (the first feature): erythema, urticaria, or angioedema.
  - Hypotension (fainting).
  - Bronchoconstriction (wheeze or hoarse voice).
- Fatal food reactions typically occur after **30–35** minutes.
- Insect stings cause shock after **10–15** minutes.
- Intravenous drug reactions occur within **5** minutes.

**Treatment**

- Apply tourniquet proximal to the site of injection if possible.
- Epinephrine **0.5 ml i.m.** (s.c. injection is slow).
  - It is the drug of choice and potentially lifesaving.
  - i.m. injection in the thigh (vastus lateralis) gives more rapid effect.
  - Repeat after 5 min if no response.
- Antihistamine (e.g. chlorpheniramine 10 mg **i.v.**).
- Hydrocortisone 200 mg **i.v** to ↓ antigen/antibody reaction.
- Intravenous fluids (0.5-1 L) and monitor BP.

## Neurogenic Shock

- Neurogenic shock is caused by **loss of sympathetic tone** of blood vessels resulting in the massive dilatation of arterioles and venules.
- It can be caused by spinal anesthesia, spinal cord injury, pain, and anxiety.

**Treatment**

- Recumbent position with head down.
- Vasopressor sympathomimetics and sedatives.

## Hypovolemic shock

**Causes**

Blood loss (hemorrhage); Plasma loss (severe burn); Water loss (vomiting, diarrhea).

**Grades of hypovolemic shock**

| | Blood loss | Response |
|---|---|---|
| **Class I** | Up to 15% (750 ml) | Compensatory mechanisms maintain BP. |
| **Class II** | 15-30% (750-1500 ml) | Hypoxia, hypotension, ↓ urine output |
| **Class III** | 30-40% (1500-2000 ml) | Profound shock with severe acidosis |
| **Class IV** | > 40% (> 2000 ml) | Coma …….. death |

**Treatment**

- I.v. fluids (Ringer solution is more superior to normal saline for use in massive hemorrhage).
- Blood transfusion
- Dopamine: to ↑ COP.

## Cardiogenic shock

**Causes**

- Acute MI
- Blunt cardiac trauma
- Myocardial depression due to any cause (drugs, infection, etc.).

**Treatment**

- All measures of treatment of acute MI (see before).
- Dobutamine i.v.i. (usually at 5 - 20 µg/kg/min).
- Lidocaine i.v. for control of ventricular arrhythmia.

## Septic shock

**Cause:** severe infection → release of inflammatory cytokines from the inflammatory cells → venodilatation (↓ venous return) and progressive tissue hypoxia.

**Treatment**

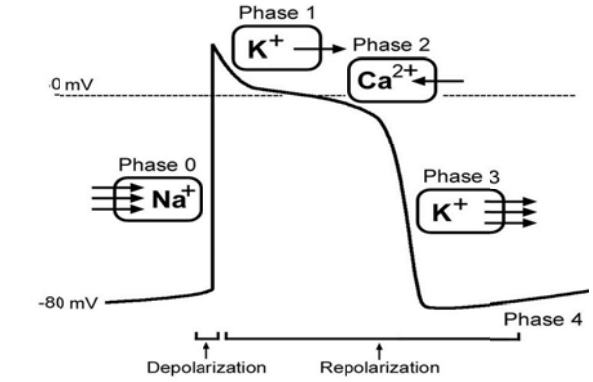
- Antibiotics according to the type of pathogen.
- Dopamine or dobutamine to ↑ COP.
- Low dose steroids to minimize toxemia.
- Oxygen if O2 saturation is <94%.

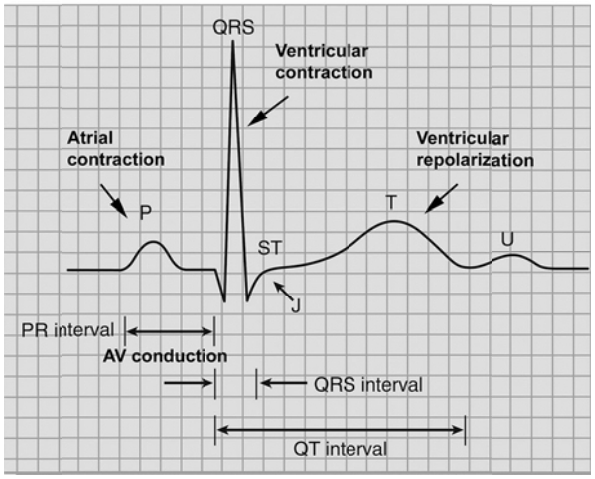
# Part 6: Cardiac arrhythmia and antiarrhythmic drugs

## Basic information

### Cardiac action potential

- In the resting state, $K^+$ ions is found mainly intracellular, while $Na^+$ and $Ca^{2+}$ are mainly extracellular making the interior of the cell electrically *negative*.
- Contraction and relaxation occur when rapid redistribution of ions across the cell membrane occurs during 4 phases known as **"action potential".**




**Phases of action potential:**

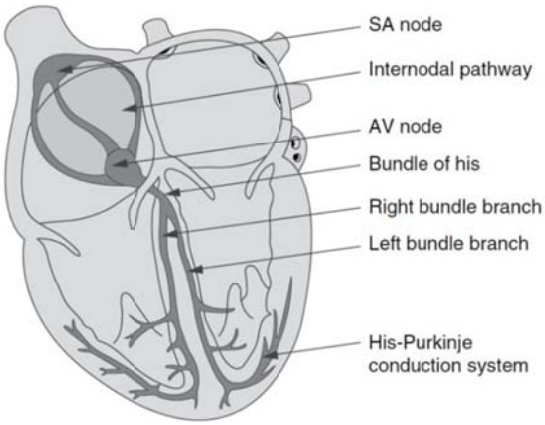
- **Phase 0:** rapid depolarization of the cell due to rapid influx of $Na^+$.
- **Phase 1:** short period of rapid re-polarization due to outflow of $K^+$.
- **Phase 2:** "plateau": delay in re-polarization due to slow influx of $Ca^{++}$.
- **Phase 3:** second period of rapid repolarization due to rapid out-flow of $K^+$.
- **Phase 4:** the resting state is restored. $Na^+$ ions are extruded out the cell and $K^+$ ions returns back by the $Na^+/K^+$ pump and so on.
- The slope of phase 4 determines when the 2nd action potential starts. When the slope is increased, the distance between 2 cardiac cycles shortens (i.e. tachycardia) and vice versa.

### Impulse formation (automaticity)

- Cardiac **automaticity** refers to the ability of certain cells to self-generate electrical impulses that spread throughout the heart.
- Under normal conditions, the **SA node** is the dominant pacemaker (i.e. has the highest automaticity).
- Normal myocardial cells don't have automaticity i.e. cannot generate impulses.
- Under certain pathologic conditions, some myocardial cells may acquire spontaneous repetitive firing, this is called **abnormal automaticity** or **ectopy**. These **ectopic** pacemakers compete with the SA node for control of the heart.

### Impulse conduction

- Electrical activity spreads from the **SA node** to the ventricles via the **AV node** and the **bundle of His**, and then down through the right and left **bundles**.
- In the **ECG**, the **P wave** represents the spread of depolarization wave through the atria (atrial contraction). The **QRS complex** represents the spread of depolarization wave through the ventricles (ventricular contraction). The **ST segment** and **T wave** represent ventricular repolarization (relaxation).




## Cardiac arrhythmia

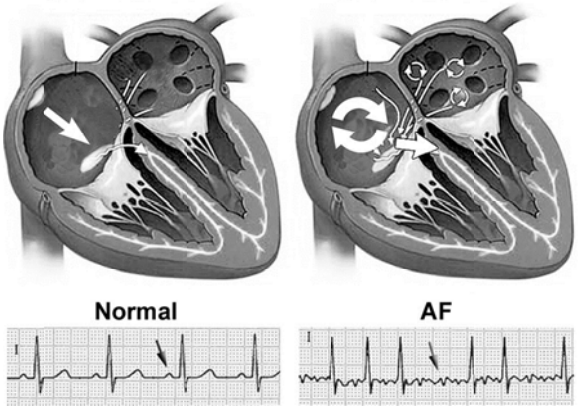
**Arrhythmia** means disturbance in the normal heart rhythm. It results from:

- Abnormal impulse generation;
- Abnormal impulse conduction;
- Both.

### Abnormal impulse formation:

- **Nodal abnormality:** e.g. sinus tachycardia and sinus bradycardia.
- **Extranodal abnormality:** e.g. premature atrial or ventricular contractions (ectopic beats).

### Abnormal impulse conduction




- **Re-entry:**

- This is a circus movement of an impulse that circulates around certain area in a unidirectional fashion and excites the conducting system more than once.
- It is the most common cause of **atrial flutter** and **fibrillation** (AF).
- Wolff–Parkinson–White syndrome (WPW) is an example of anatomically defined re-entry. WPW syndrome is an atrioventricular re-entrant tachycardia, secondary to an accessory AV conducting pathway (see before).

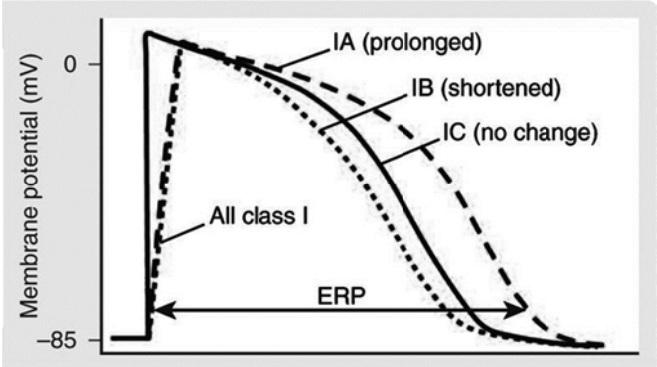
- **Heart block:**

– AV conduction is **delayed** (first degree), **intermittent** (second degree), or **completely blocked** (third degree).

## ANTIARRHYTHMIC DRUGS

- Antiarrhythmic drugs produce effects by altering one or more of the following factors: 1) Automaticity; 2) Conduction velocity; 3) Refractory period; 4) Membrane responsiveness.
- Almost all antiarrhythmic drugs have more than one mechanism of action. The simplified **Vaughan Williams classification system** assumes that each drug has **one main** mechanism of action:

**Class I: Na⁺ channel blockers:**




- **Class IA: e.g. quinidine, procainamide, disopyramide**: moderately block **Na⁺** channels and ↑ ERP (effective refractory period) and APD (action potential duration)
- **Class IB: e.g. lidocaine, mexiletine:** weakly block **Na⁺** channels and ↓ ERP and APD.
- **Class IC: e.g. flecainide, propafenone:** strongly block **Na⁺** and **K⁺** channels with no effect on ERP or APD.

**Class II: Beta-blockers: e.g. propranolol, bisoprolol, metoprolol**

They ↓ AV conduction and inhibit phase 4 depolarization.

**Class III: K⁺ channel blockers: e.g. amiodarone, dronedarone, ibutilide, sotalol**

They inhibit mainly **K⁺** channels and ↑ ERP.

**Class IV: Ca⁺ channel blockers: e.g. verapamil and diltiazem**

They inhibit mainly **$Ca^{2+}$** channels and ↑ ERP.

**Other unclassified drugs: digoxin, adenosine, Mg sulphate**

## Quinidine (subclass 1A)

### Mechanism and pharmacological effects

- It blocks **activated $Na^+$** channels leading to decrease the rate of phase-0 depolarization, decrease excitability, and ↑ APD and ERP.
- It blocks **muscarinic** and **α** receptors leading to atropine-like action (vagolytic) and hypotension.
- Quinidine has complex effect on **AV conduction** due to direct and vagolytic actions:
  - At low doses: its vagolytic action predominates → ↑ AV conduction.
  - At therapeutic doses: its direct action predominates → ↓ AV conduction
- It has –ve inotropic effect and antimalarial effect (against *P. falciparum*).

### Therapeutic uses

- Quinidine was used for many years to treat **supraventricular** and **ventricular** arrhythmias, and to **maintain** sinus rhythm after conversion from atrial flutter and fibrillation; however, it is **rarely** used today because of availability of more effective and less toxic drugs.

### Adverse effects and precautions

- **Cinchonism:** tinnitus (i.e. hearing of ringing or hiss), headache, blurred vision, vomiting, and diarrhea.
- **Hypotension:** after rapid i.v. infusion due to α-receptors blockade.
- **Paradoxical tachycardia:** quinidine has atropine-like action and, it may ↑ AV conduction and cause "*paradoxical tachycardia*". Digitalis or verapamil should be given before quinidine to offer rate control by ↓ AV conduction.
- **Quinidine syncope:** quinidine ↑ QT interval and may predispose the patient to a serious type of arrhythmia *(torsade de pointes).* Quinidine therefore should not be given to patients with long QT syndrome or with other drugs that ↑ QT interval.

## Procainamide (subclass 1A)

- This drug is equivalent to quinidine as an antiarrhythmic agent and has similar cardiac and toxic effects. Like quinidine, its use now is very **limited.**
- **Additional adverse effect:** procainamide is metabolized by hepatic acetylation; 30% of patients (slow acetylators) develop drug-induced systemic lupus erythematosus (SLE) after long term therapy.

**Drug-induced SLE like syndrome**

Hydralazine (+++)
Procainamide (++)
Isoniazid (+)
Quinidine (+)
Phenytoin (+)

### Lidocaine (subclass 1B)

- Lidocaine (lignocaine) is exclusively **$Na^+$ channel blocker**; it is highly selective for damaged tissues.
- It undergoes extensive first-pass metabolism so, it is **not given orally**.
- It is given only **i.v.** for acute suppression of ventricular arrhythmia associated with **acute MI** (not for long-term treatment). The usual dose is 50-100 mg i.v. half of this dose may be repeated after 5-10 min if necessary.
- It has **no effect** on AV conduction, so it is **not used** for supraventricular arrhythmia.
- Most adverse effects are **neurologic**.

**N.B.**

- **Mexiletine** is very similar to lidocaine but can be given **orally**. It is used primarily for long-term treatment of ventricular arrhythmias associated with **previous MI**.
- **Phenytoin** is antiepileptic drug with class 1B activity. It is used primarily in the treatment of **digitalis-induced tachyarrhythmia**. It has a limited role in the treatment of other ventricular arrhythmias. The IV loading dose is 250 mg given over 10 minutes.

### Flecainide (subclass 1C)

- It blocks both **$Na^+$** and **$K^+$** channels leading to decrease the rate of phase-0 depolarization and **slows AV conduction**. Due to its complex effects on cardiac tissue, the APD is **not altered**.
- It is used for atrial and ventricular arrhythmia and for maintenance sinus rhythm after conversion from atrial flutter and fibrillation.
- Flecainide increases the incidence of ventricular fibrillation and sudden death after MI (proarrhythmic effect), so it is **contraindicated** for patients with ischemic heart disease or structural heart disease (e.g. LV hypertrophy).

## Class II: Beta blockers

### Mechanism of action

They ↓ sympathetic stimulation, inhibit phase 4 depolarization, depress automaticity, prolong AV conduction, ↑ heart rate and ↓ contractility.

### Therapeutic uses

- All arrhythmia induced by sympathetic overactivity.
- Arrhythmia due to thyrotoxicosis.

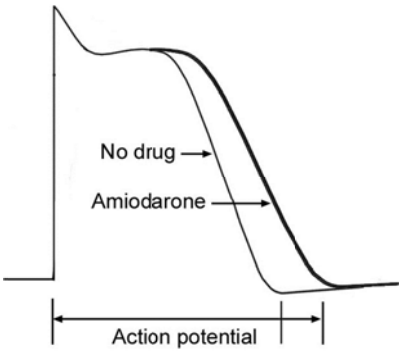
- Arrhythmia associated with HOCM.
- Supraventricular arrhythmia (AF).
- Arrhythmia due to mitral valve prolapse.

## Class III: Amiodarone

- It is structurally related to thyroxine. It contains ~ 40% iodine. **Dronedarone** is chemically similar to amiodarone but does not contain iodine.
- Amiodarone has **long t½** and **large Vd** so, it can accumulate in many tissues leading to wide range of adverse effects.

### Mechanism of action

- Blocks mainly **$K^+$** channels → slowing of phase 3 → ↑ ERP.
- Blocks **$Na^+$** channels → ↓ excitability.
- Blocks **$Ca^{2+}$** channels → – ve inotropic and chronotropic effects.




### Therapeutic uses: (most types of arrhythmia)

- Supraventricular and ventricular arrhythmia.
- WPW syndrome.
- Arrhythmia resistant to other drugs.

### Adverse effects

- Dose-related **pulmonary toxicity** (fibrosis) is the most important adverse effect.
- **Hepatic** toxicity.
- **Thyroid dysfunction**: hypo- or hyperthyroidism because of its iodine content.
- **Corneal microdeposits:** reversible, does not affect vision.
- **Bradycardia** and heart block.
- **Photosensitivity** leading to gray-blue skin discoloration in sun-exposed areas.

Chest x-ray in an elderly patient on amiocarone demonstrates numerous reticular opacities most marked in the right upper zone

## Class IV: CCBs (verapamil and diltiazem)

**Mechanism of action:** They ↓ SAN activity and AV conduction

### Therapeutic uses

- Non-dihydropyridines (verapamil and diltiazem) are primarily used to reduce HR in **supraventricular tachycardia** (SVT) and arrhythmia associated with HOCM.
- CCBs have **no role** in the chronic management of **ventricular tachycardia** (VT). IV verapamil should **never be used** in the acute management of VT, as it may cause hemodynamic collapse.

## Other antiarrhythmic agents: Adenosine

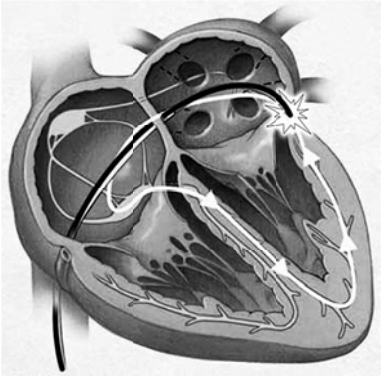
- It is a purinergic **A1 receptor agonist**; this leads to opening of $K^+$ channels and inhibition of $Ca^{2+}$ channels (i.e. hyperpolarization) in the AV conducting system and directly **inhibits AV nodal conduction**.
- It has very short half-life of 8-10 seconds.
- It is the drug of choice for immediate termination of paroxysmal supraventricular tachycardia (including WPW syndrome). It is given as a bolus dose of 6 mg i.v. followed, if necessary, by a dose of 12 mg.
- The drug is less effective in the presence of adenosine receptor blockers such as **theophylline** or caffeine.
- It is contraindicated in patients with **asthma** because it can cause **bronchospasm**.

## Non-pharmacological methods

### DC cardioversion

- It is application of direct current (electric shock) to the chest wall for **emergency** control of any type of arrhythmia especially **rapid AF** in an unstable patient (i.e. hypotensive).
- The patient should be **heparinized** before the procedure.
- Following electrical cardioversion, patients should be anticoagulated for at least 4 weeks.

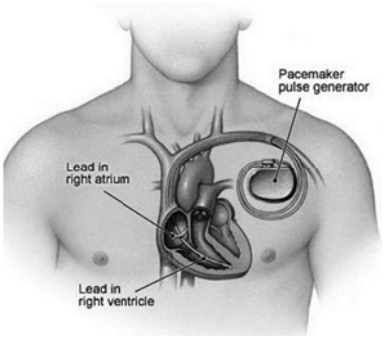
### Laser ablation



- It is used for many types of arrhythmias.
- A catheter is inserted into a specific area of the heart. A special machine directs energy through the catheter to small areas of the heart muscle that causes the abnormal heart rhythm. This energy "disconnects" the pathway of the abnormal rhythm.
- Laser radiofrequency ablation is the definite treatment of **WPW syndrome**.

**Artificial pacemakers and implantable cardioverter defibrillators**

- They are battery-powered electronic devices that are implanted under the skin or in the chest cavity to monitor and pace the heart.




## Management of cardiac arrest

Cardiac arrest involves cessation of cardiac **mechanical** activity as confirmed by absence of signs of circulation (absent pulse and apnea).

### Causes

- Coronary heart disease (~80%).
- Cardiac disease: e.g. HOCM, Brugada syndrome.
- Cardiac arrhythmia especially ventricular.
- Others: trauma, electrolyte imbalance, electrical shock, drugs, etc.

### Patterns of arrest

- Complete asystole: the ECG is flat line.
- Ventricular fibrillation: ECG shows fibrillation waves.
- Pulseless electrical activity (PEA): There is some electrical activity (other than VF) without detectable pulse.

### Management

- The ultimate goal of treatment is to preserve life by early CPR 30:2 i.e. cycles of 30 chest compressions followed by 2 rescue breaths.
- Administer electrical defibrillation at 360J then repeat CPR for 2 min.
  → No response → **Epinephrine** 1 mg i.v. /3-5 min with CPR.
  → No response → DC shock with CPR for 2 min.
  → No response → **Amiodarone** 300 mg i.v. with CPR.
  → No response → DC shock with CPR.

  **Shock –** Drug **– Shock –** Drug **– Shock**

Notes

Clinical
Pharmacology
Department

Mansoura Faculty of Medicine

## Review Questions

**Mention the pharmacodynamic principles underlying the use of:**

- Verapamil in angina pectoris
- Verapamil in hypertrophic obstructive cardiomyopathy
- Nifedipine in arterial hypertension
- Lisinopril in arterial hypertension
- Captopril in diabetic nephropathy
- Nitroglycerine in angina pectoris
- Digoxin in congestive heart failure

**Mention the pharmacodynamic principles underlying the contraindication of:**

- Nifedipine in supraventricular tachycardia
- Verapamil in Wolff-Parkinson-White syndrome
- Captopril in hypertension associated with severe chronic renal failure
- Digoxin in heart failure associated with heart block
- Beta-blockers in Prinzmetal's (variant) angina

**Mention the precautions underlying the use of:**

- Nitrates in angina pectoris
- ACEIs in hypertension
- Quinidine in atrial arrhythmia

**Mention the essential lines of treatment of the following emergency conditions:**

- Acute severe arterial hypertension
- Acute pulmonary edema
- Acute myocardial infarction
- Acute anaphylactic shock

**Mention 3 side effects of each of the following drugs:**

- Verapamil
- Captopril
- Isosorbide dinitrate
- Amiodarone

**Mention the rational of the following combinations:**

- Nitrates with beta-blockers in angina pectoris
- Hydralazine with diuretics in systemic hypertension
- Captopril with furosemide in arterial hypertension

**Mention the main differences between:**

- Verapamil and nifedipine
- Digitalis and quinidine
- Captopril and lisinopril

**Of each of the following questions, select THE BEST SINGLE answer:**

**1. The followings drugs given alone are useful for treatment of hypertension EXCEPT:**
**A.** Amiodarone.
**B.** Propranolol.
**C.** Captopril
**D.** Furosemide
**E.** Verapamil

**2. Significant relaxation of arteriolar and venular smooth muscles can be pro-duced by which of the following drugs:**
**A.** Hydralazine
**B.** Minoxidil
**C.** Diazoxide
**D.** Sodium nitroprusside
**E.** Nifedipine

**3. One of the following drugs is effective in treatment of ischemic episodes in patients with variant angina:**
**A.** Propranolol
**B.** Nitroglycerine
**C.** Sodium nitroprusside
**D.** Diltiazem
**E.** Hydralazine

**4. The following is true about calcium channel blockers:**
**A.** Verapamil has a positive inotropic effect
**B.** Verapamil dilates coronary arteries more than nifedipine
**C.** Verapamil effectively relieves A-V block
**D.** Diltiazem may cause ankle edema
**E.** Nifedipine is contraindicated in Raynaud's disease

**5. Negative inotropy and chronotropy are most prominent with the use of the following drug:**
**A.** Nifedipine
**B.** Nicardipine
**C.** Nimodipine
**D.** Diltiazem
**E.** Verapamil

**6. Which of the following mechanisms best explains the antihypertensive actions of clonidine:**
**A.** Blockade of β1 adrenergic receptors
**B.** Blockade of α1 adrenergic receptors
**C.** Blockade of central α2 receptors
**D.** Stimulation of presynaptic α2 receptors
**E.** Stimulation of presynaptic β2 receptors

**7. When glyceryl trinitrate (nitroglycerine) tablets are prescribed for angina pectoris, the patient should be told:**
**A.** To take it to prevent pain
**B.** To take it at the onset of pain
**C.** That if throbbing headache and palpita-tion occur the patient should take another
**D.** That if he feels faint he should stand up perfectly
**E.** To keep the tablet in a warm humid place e.g. a shelf over the bath

**8. Which of the following antihypertensive drugs may cause fetal pulmonary hypoplasia and growth retardation if used during pregnancy:**
**A.** Hydralazine
**B.** Alpha-methyldopa
**C.** Atenolol
**D.** Clonidine
**E.** Captopril

**9. All the following statements are true for nitroglycerine EXCEPT:**
**A.** Can cause adverse reactions of headache and tachycardia
**B.** Undergoes significant first-pass biotransformation
**C.** Can be used i.v. for the treatment of acute heart failure
**D.** Has duration of action of several hours after sublingual administration
**E.** Can increase exercise tolerance if taken immediately before exercise

**10. A 57-year-old man is being treated for an atrial arrhythmia. He complains**

**of headache, dizziness, and tinnitus. Which one of the following antiarrhythmic drugs is the most likely cause?**

**A.** Quinidine.
**B.** Amiodarone.
**C.** Procainamide.
**D.** Propranolol.
**E.** Verapamil

**11. A 58-year-old woman is being treated for chronic suppression of a ventricular arrhythmia. After 2 months of therapy, she complains about feeling tired all the time. Examination reveals a resting heart rate of 10 beats per minute lower than her previous rate. Her skin is cool and clammy. Laboratory test results indicate low thyroxin and elevated thyroid-stimulating hormone levels. Which of the following antiarrhythmic drugs is the likely cause of these signs and symptoms?**

**A.** Amiodarone.
**B.** Procainamide.
**C.** Propranolol.
**D.** Quinidine.
**E.** Verapamil.

**12. A 56-year-old patient complains of chest pain following any sustained exercise. He is diagnosed with atherosclerotic angina. He is prescribed sublingual nitroglycerin for treatment of acute chest pain. Which of the following adverse effects is likely to be experienced by this patient?**

**A.** Hypertension.
**B.** Throbbing headache.
**C.** Bradycardia.
**D.** Sexual dysfunction.
**E.** Anemia.

**13. A 68-year-old man has been successfully treated for exercise-induced angina for several years. He recently has been complaining about being awakened at night with chest pain. Which of the following drugs would be useful in preventing this patient's nocturnal angina?**

**A.** Amyl nitrite.
**B.** Nitroglycerin (sublingual).
**C.** Nitroglycerin (transdermal).
**D.** Esmolol.
**E.** Hydralazine.

**14. Compensatory increases in heart rate and renin release that occur in heart failure may be alleviated by which of the following drugs?**

**A.** Milrinone.
**B.** Digoxin.
**C.** Dobutamine.
**D.** Enalapril.
**E.** Metoprolol.

**15. A 58-year-old man is admitted to the hospital with acute heart failure and pulmonary edema. Which one of the following drugs would be most useful in treating the pulmonary edema?**

**A.** Digoxin.
**B.** Dobutamine.
**C.** Furosemide.
**D.** Minoxidil.
**E.** Spironolactone.

**16. A 45-year-old man has recently been diagnosed with hypertension and started on monotherapy designed to reduce peripheral resistance and prevent NaCl and water retention. He has developed a persistent cough. Which of the following drugs would have the same benefits but would not cause cough?**

**A.** Losartan.
**B.** Nifedipine.
**C.** Prazosin.
**D.** Propranolol.
**E.** Verapamil.

**17. Which one of the following drugs may cause a precipitous fall in blood pressure and fainting on initial administration?**

**A.** Atenolol.
**B.** Hydrochlorothiazide.
**C.** Nifedipine.
**D.** Prazosin.
**E.** Verapamil.

**18. Which one of the following antihypertensive drugs can precipitate a hypertensive crisis following abrupt cessation of therapy?**

**A.** Clonidine.
**B.** Diltiazem.
**C.** Enalapril.
**D.** Losartan.
**E.** Hydrochlorothiazide.

**19. Which of the following statements is most correct regarding the use of drugs in hypertension?**

**A.** beta-blockers are contraindicated if hypertension is associated with heart failure
**B.** calcium channel blockers are contraindicated if the patient also has obstructive pulmonary disease
**C.** diuretics are contraindicated in hypertension associated with diabetes
**D.** vasodilators are contraindicated in a patient taking a diuretic
**E.** ACE inhibitors are contraindicated if the patient is pregnant

**20. β-Blockers have been effective in the treatment of heart failure. They primarily exert their effect by:**

**A.** Binding to the receptor that binds norepinephrine
**B.** Inducing a prominent diuretic effect
**C.** Increasing contractility
**D.** Improving asthma control
**E.** Increasing heart rate to meet the additional demands placed upon the heart in CHF

**21. A patient has periodic episodes of paroxysmal supraventricular tachycardia (PSVT). Which of the following drugs would be most suitable for outpatient prophylaxis of these worrisome electrophysiologic events?**

**A.** Adenosine
**B.** Lidocaine
**C.** Nifedipine
**D.** Nitroglycerin
**E.** Verapamil

**22. We prescribe a beta-adrenergic blocker for a patient with chronic-stable ("effort-induced") angina, and the incidence and severity of anginal attacks are reduced. Which of the following best explains the pharmacologic action by which the beta blocker does this?**

**A.** Decreases myocardial oxygen demand
**B.** Dilates the coronary vasculature
**C.** Exerts antiplatelet/antithrombotic effects
**D.** Reduces total peripheral resistance
**E.** Slows AV nodal conduction velocity

**23. Your patient is a 50-year-old man with essential hypertension and no other complications. Which of the following drugs would be the most rational first choice for starting his antihypertensive therapy?**

**A.** Angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker
**B.** Beta-adrenergic blocker
**C.** Nifedipine
**D.** Thiazide diuretic
**E.** Verapamil or diltiazem

**24. We have a 50-year-old man with asymptomatic hyperuricemia, and we are about to start therapy for newly diagnosed essential hypertension (BP 136/90 mm Hg, based on repeated measurements with the patient supine and at rest). Which of the following antihypertensive drugs is most likely to increase his serum uric acid levels further, and possibly precipitate a gout attack?**

**A.** Captopril
**B.** Hydrochlorothiazide
**C.** Labetalol
**D.** Losartan
**E.** Verapamil

**25. We've just diagnosed essential hypertension in a 58-year-old female patient. She tends to be tachycardic. Notes written by her ophthalmologist indicate that she has chronic open-angle glaucoma. Which of the following drugs would be the most rational**

**choice for this woman, given only the information presented in this question?**

**A.** Captopril
**B.** Diltiazem
**C.** Hydrochlorothiazide
**D.** Timolol
**E.** Verapamil

**26. Our newly diagnosed hypertensive patient has a history of vasospastic angina. Which of the following drugs or drug classes would be the most rational for starting antihypertensive therapy because it exerts antihypertensive effects, directly lowers myocardial oxygen demand and consumption, and also tends to inhibit cellular processes that otherwise favor coronary vasospasm?**

**A.** Angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker
**B.** Beta-Adrenergic blocker
**C.** Nifedipine
**D.** Thiazide diuretic
**E.** Verapamil (or diltiazem)

**27. Quinidine is ordered for a patient with recurrent atrial fibrillation and who refuses any interventions other than drugs in an attempt to terminate and control the arrhythmia. Which of the following is the most likely effect of quinidine?**

**A.** Is likely to increase blood pressure via a direct vasoconstrictor effect
**B.** Is contraindicated if the patient also requires anticoagulant therapy
**C.** Slows spontaneous SA nodal depolarization as its predominant effect
**D.** Tends to slow electrical impulse conduction velocity through the AV node
**E.** Will increase cardiac contractility (positive inotropic effect) independent of its antiarrhythmic effects

**28. A patient who has been taking an oral antihypertensive drug for about a year develops a positive Coombs' test. Which of the following drugs is the most likely cause?**

**A.** Captopril
**B.** Clonidine
**C.** Labetalol
**D.** Methyldopa
**E.** Prazosin

**29. A patient has Stage III essential hypertension. After evaluating the responses to several other antihypertensive drugs, alone and in combination, the physician places the patient on oral hydralazine. Which of the following adjunct(s) is/are likely to be needed to manage the expected and unwanted cardiovascular side effects of the hydralazine?**

**A.** Captopril plus nifedipine
**B.** Digoxin plus spironolactone
**C.** Digoxin plus vitamin K
**D.** Hydrochlorothiazide and a beta blocker
**E.** Triamterene plus amiloride

**30. At high (but not necessarily toxic) blood levels, a cardiovascular drug causes lightheadedness, tinnitus, and visual disturbances such as diplopia. What is the most likely drug that caused these responses?**

**A.** Atropine
**B.** Captopril
**C.** Dobutamine
**D.** Propranolol
**E.** Quinidine

**31. We have a patient who is diagnosed with variant (vasospastic) angina. Which of the following drugs would be most appropriate, and generally regarded as most effective, for long-term therapy aimed at reducing the incidence or severity of the coronary vasospasm?**

**A.** Aspirin
**B.** Atorvastatin
**C.** Diltiazem
**D.** Nitroglycerin
**E.** Propranolol

**32. The following treatments can be applied for rapid relief of acute anginal pain EXCEPT:**
**A.** Sublingual nitroglycerine
**B.** Sublingual isosorbide dinitrate
**C.** Oral aspirin
**D.** Inhaled amylnitrite
**E.** Intravenous nitroglycerine

**33. Which of the following statements is true concerning the action of enalapril:**
**A.** It is prodrug for an angiotensin II blocker
**B.** Stimulates angiotensin II receptors
**C.** Increases endogenous bradykinin levels
**D.** Does not lower blood pressure in "normal renin" hypertension
**E.** Best indicated to patients with hypertension associated with liver disease

**34. Beta-blockers are considered the first choice in the control hypertension in the following cases EXCEPT:**
**A.** Hypertension with thyrotoxicosis
**B.** Hypertension with ventricular premature beats
**C.** Hypertension with variant angina
**D.** Hypertension with high plasma renin
**E.** Young patient with increased sympathetic activity

**35. Severe myocardial pain due to acute inferior MI with excessive vagal stimulation can be best managed by:**
**A.** Morphine
**B.** Meperidine
**C.** Butorphanol
**D.** Diclofenac
**E.** Indomethacin

**36. The enhancement of myocardial contractility after digitalis is due to:**
**A.** Increased cyclic AMP
**B.** Stimulation of calmodulin
**C.** Beta-adrenergic stimulation
**D.** Increased production of adenosine
**E.** Inhibition of the sodium pump

**37. An ideal drug for treatment of ventricular arrhythmia due to acute myocardial infarction is:**
**A.** Propranolol
**B.** Lidocaine
**C.** Quinidine
**D.** Procainamide
**E.** Verapamil

**38. Digoxin is not indicated to treat heart failure as long systemic hypertension is present because:**
**A.** The heart may develop more strain and failure
**B.** Absorption of digoxin will be reduced
**C.** Excretion of digoxin will be reduced
**D.** Liability for digoxin toxicity is high with hypertension
**E.** Systemic hypertension will be reduced suddenly

**39. Wolff-Parkinson-White syndrome can be successfully treated by:**
**A.** Quinidine
**B.** Verapamil
**C.** Atenolol
**D.** Digoxin
**E.** Amiodarone

**40. All the following are positive inotropic drugs EXCEPT:**
**A.** Digitalis
**B.** Adrenaline
**C.** Aminophylline
**D.** Dopamine
**E.** Amiodarone

**41. All the following are class I antiarrhythmic drugs EXCEPT:**
**A.** Lidocaine
**B.** Quinidine
**C.** Propranolol
**D.** Phenytoin
**E.** Procainamide

**42. Which of the following cardiac glycosides has the clearly higher therapeutic index:**
**A.** Ouabain.
**B.** Digoxin.
**C.** Digitoxin.

**D.** Deslanoside
**E.** None of the above

**43. The ECG of a patient who is receiving digitalis in the therapeutic range would be most likely to show:**
**A.** Prolongation of the QT interval.
**B.** Prolongation of the PR interval.
**C.** Symmetrical peaking of the T-wave
**D.** Widening of the QRS complex
**E.** Deep Q wave

**44. If both quinidine and digoxin are administered concurrently, which of the following effects does quinidine have on digoxin?**
**A.** The absorption of digoxin from the GIT is decreased
**B.** The metabolism of digoxin is prevented
**C.** The concentration of digoxin in the plasma is increased
**D.** The excretion of digoxin is increased
**E.** The ability of digoxin to inhibit $N^+/K^+$ ATPase is reduced

**45. All of the following are considered mechanisms of antiarrhythmic drugs EXCEPT:**
**A.** Calcium channel blockade
**B.** Inhibition of catecholamine action on the heart
**C.** Sodium channel blockade
**D.** Increasing the slope of phase 4 depolarization
**E.** Prolongation of effective refractory period (action potential duration)

**46. All the following are side effects of amiodarone EXCEPT:**
**A.** Corneal microdeposits
**B.** Tachycardia
**C.** Thyroid dysfunction
**D.** Pulmonary infiltration
**E.** Hepatotoxicity

**47. Digitalis toxicity is enhanced by which one of the following:**
**A.** Decreased extracellular Ca++
**B.** Decreased stimulation rate
**C.** Increased extracellular Mg++
**D.** Decreased extracellular K+
**E.** Decreased extracellular $Na^+$

**48. The most specific line for treatment of digitalis toxicity is:**
**A.** Stop digitalis administration
**B.** Administration of potassium
**C.** Administration of Fab fragments
**D.** Administration of phenytoin
**E.** Administration of calcium

**49. The usefulness of digitalis in management of atrial fibrillation depends on its ability to:**
**A.** Decrease atrial impulse formation
**B.** Decrease vagal control over the heart
**C.** Decrease conduction time through the A-V node
**D.** Increase the effective refractory period of the A-V node
**E.** Increase conduction time in the atria

**50. Quinidine is either contraindicated or should be used with caution in all of the following EXCEPT:**
**A.** Complete atrioventricular block.
**B.** Digitalis intoxication
**C.** Severe congestive heart failure
**D.** Atrial fibrillation of recent origin
**E.** History of idiosyncrasy due to quinidine

**51. A 45-year-old man asks his physician for a prescription for sildenafil to improve his sexual performance. Because of risks from a serious drug interaction, this drug should not be prescribed, and the patient should be urged not to try to obtain it from other sources, if he is also taking which of the following drugs?**
**A.** An angiotensin-converting enzyme inhibitor
**B.** A beta-adrenergic blocker
**C.** A nitrovasodilator (e.g., nitroglycerin)
**D.** A statin-type antihypercholesterolemic drug
**E.** A thiazide or loop diuretic

**52. A 70-year-old woman is treated with sublingual nitroglycerin for occasional bouts of effort-induced angina. Which of the following best describes the mechanism by which nitroglycerin causes its desired antianginal effects, or a mediator involved in it?**

**A.** Blocks beta adrenergic receptors
**B.** Forms cyanide, much like the metabolism of nitroprusside does
**C.** Increases local synthesis and release of adenosine
**D.** Raises intracellular cGMP levels
**E.** Stimulates phosphodiesterase

**53. All of the following are recommended at the initial stages of treating patients with heart failure EXCEPT:**

**A.** Reduced salt intake
**B.** Verapamil
**C.** ACE inhibitors
**D.** Diuretics
**E.** Vasodilators

**54. Which one of the following drugs increases digoxin plasma concentration by a pharmacokinetic mechanism?**

**A.** Captopril
**B.** Hydrochorothiazide
**C.** Lidocaine
**D.** Quinidine
**E.** Sulfasalazine

**55. Regarding verapamil, which one of the following statements is false?**

**A.** Angina pectoris is an important indication for the use of verapamil
**B.** Contraindicated in the asthmatic patient
**C.** Relaxes vascular smooth muscle
**D.** Slows the depolarization phase of the action potential in AV nodal cells
**E.** Used in management of supraventricular tachycardias

**56. Exertion–induced angina, which is relieved by rest, nitroglycerin, or both, is referred to as:**

**A.** Prinzmetal's angina
**B.** Unstable angina
**C.** Classic angina
**D.** Variant angina
**E.** Preinfarction angina

**57. Which of the following drugs is a class IV antiarrhythmic that is primarily indicated for the treatment of supraventricular tachyarrhythmias?**

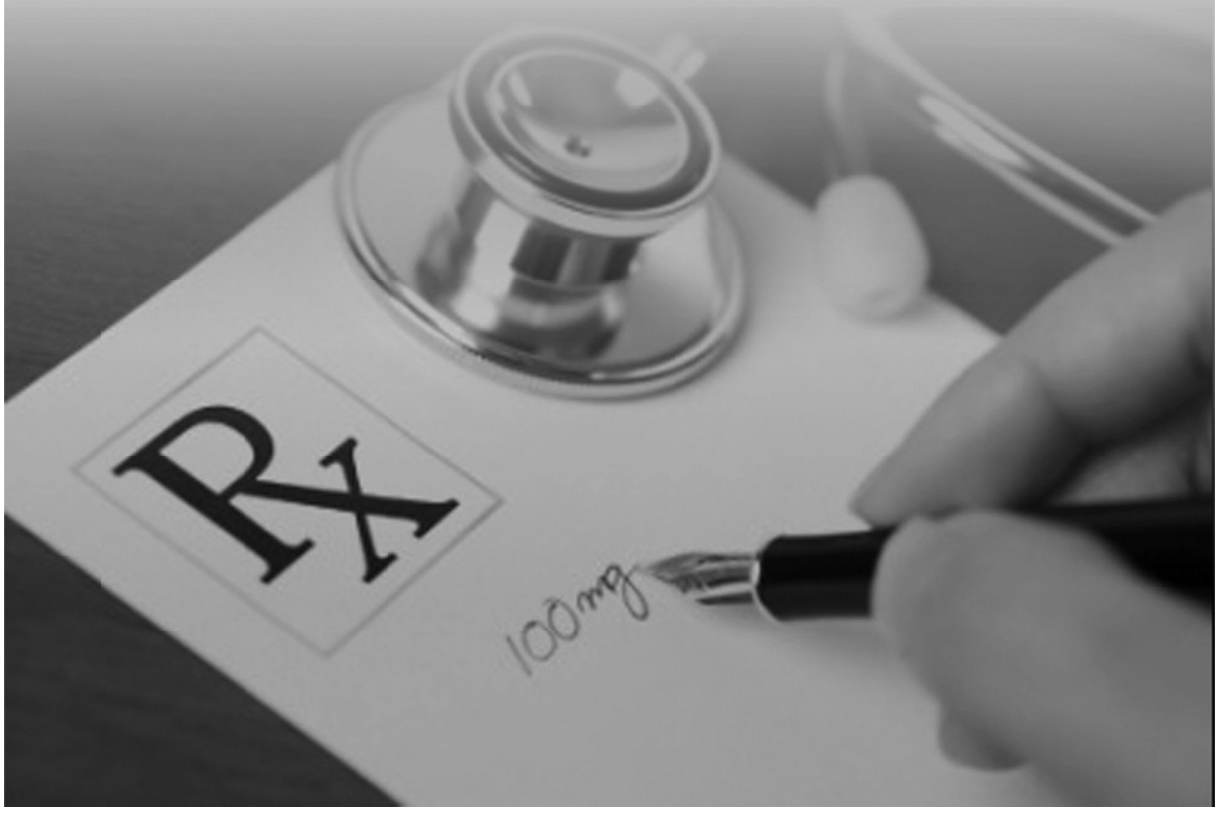
**A.** Diltiazem
**B.** Digoxin
**C.** Mexiletine
**D.** Quinidine
**E.** Propranolol

**Answers**

| | | | | |
|---|---|---|---|---|
| 1 A | 13 C | 25 D | 37 B | 49 D |
| 2 D | 14 E | 26 E | 38 A | 50 D |
| 3 D | 15 C | 27 C | 39 E | 51 C |
| 4 D | 16 A | 28 D | 40 E | 52 D |
| 5 E | 17 D | 29 D | 41 C | 53 B |
| 6 D | 18 A | 30 E | 42 E | 54 D |
| 7 B | 19 E | 31 C | 43 B | 55 B |
| 8 E | 20 A | 32 C | 44 C | 56 C |
| 9 D | 21 E | 33 C | 45 D | 57 A |
| 10 A | 22 A | 34 C | 46 B | |
| 11 A | 23 D | 35 B | 47 D | |
| 12 B | 24 B | 36 E | 48 C | |

# Chapter 6

# Pharmacology Of The Blood



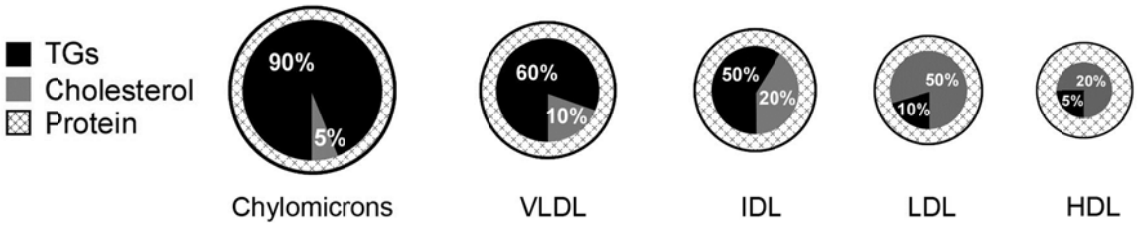
# Chapter 6

# Pharmacology Of The Blood

## Part 1: Hyperlipidemia and drugs that lower plasma lipids

### Basic information

- **Lipoproteins** consist of a hydrophobic lipid core (TGs or cholesterol) surrounded by a hydrophilic coat of phospholipids and proteins (apoproteins), which render them miscible in aqueous plasma.
- There are **5** classes of lipoproteins depending on their relative proportion of the core lipids, type of apoprotein, size, and density:



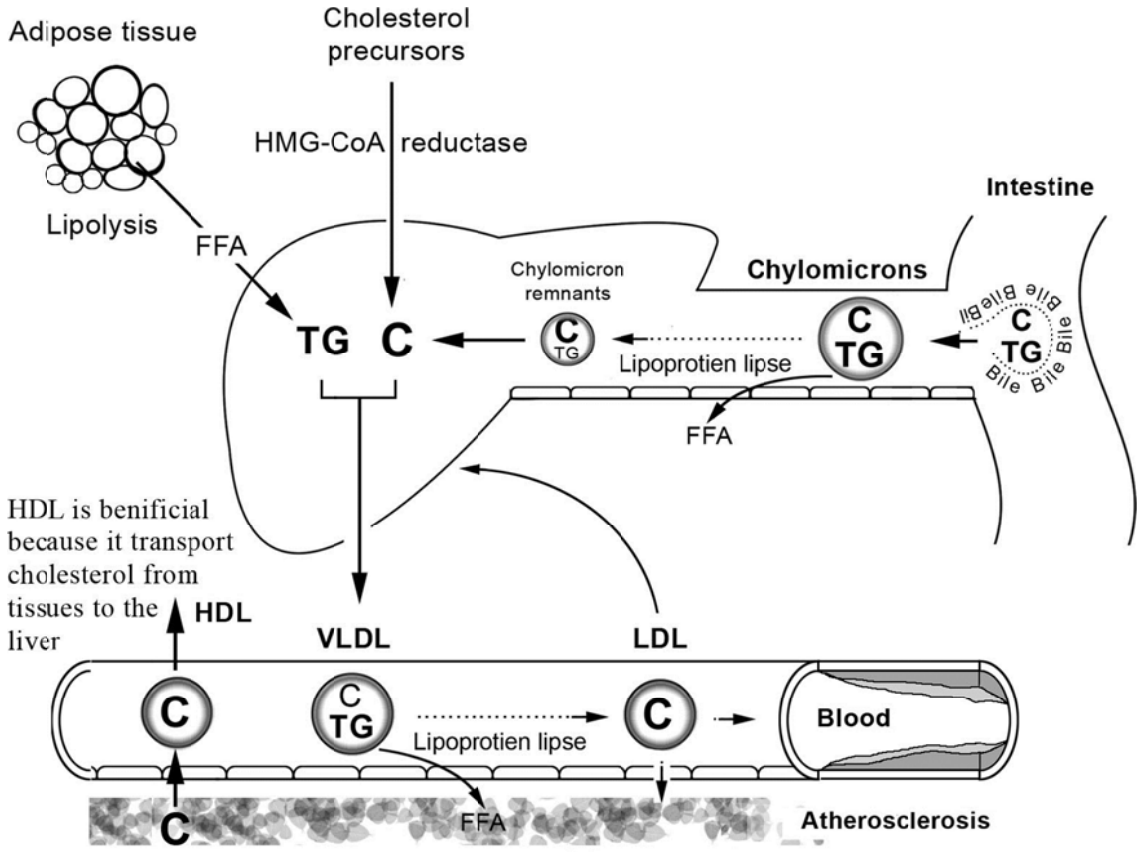

- The **intestine** is the main *source* of lipid precursors. The **liver** is the main site of *synthesis* of lipoproteins. The **adipose tissue** is the main site of *storage* of TGs. Fat cells don't synthesize any lipoproteins.

### Lipoprotein metabolism

- **In the exogenous pathway**, absorbed cholesterol and TGs are transported in plasma as **chylomicrons**. On the vascular endothelium, the core TGs is hydrolyzed by a surface-bound *lipoprotein lipase* into FFA which enter the tissue and utilized. The chylomicrons **remnants** (containing mainly cholesterol) pass to the liver where cholesterol is stored, oxidized to bile acids, or secreted in the bile. Alternatively, it may enter the synthesis of **VLDL**.
- **In the endogenous pathway**, cholesterol and newly synthesized TGs are assembled as **VLDL** and delivered to the blood where TGs core is hydrolyzed by

*lipoprotein lipase* into FFA as described above. The smaller VLDL particles having less TGs and more cholesterol are now termed **LDL**. Cholesterol in the LDL may be: (1) utilized by the tissues; (2) returns again to the liver; (3) deposited subintimal in blood vessels and cause **atherosclerosis**.

- When cells **die**, cholesterol in their plasma membranes is returned to the liver as plasma **HDL** particles. HDL functions as scavenger lipoproteins.




## Classification of hyperlipidemia

- **Primary (familial; hereditary) hyperlipidemia:** is genetically determined.

| Class | Increased lipoprotein | Synonym |
|---|---|---|
| **Type I** | ↑ chylomicrons | Familial chylomicronemia |
| **Type IIa** | ↑ LDL | Familial hypercholesterolemia |
| **IIb** | ↑ LDL and VLDL | Familial combined hyperlipidemia |
| **Type III** | ↑ IDL | Familial dysbetalipoproteinemia |
| **Type IV** | ↑ VLDL | Familial hypertriglyceridemia |
| **Type V** | ↑ VLDL and chylomicrons | Familial mixed hyperlipedemia |

- **Secondary (acquired) hyperlipidemia:**
  - Hypercholesterolemia: hypothyroidism, nephrotic syndrome, and drugs.
  - Hypertriglyceridemia: DM, alcohol, gout, chronic renal failure.

## LIPID LOWERING DRUGS

### Classification of drugs

- **Inhibitors of intestinal cholesterol absorption:**
  - Bile acid binding resins: cholestyramine, colestipol
  - Ezetimibe
- **Activators of plasma lipoprotein lipase:** fibric acid derivatives
- **HMG-CoA reductase inhibitors:** statins.
- **Inhibitors of hepatic lipid production:** nicotinic acid, acipimox
- **Other drugs:** d-thyroxin, neomycin, and probucol

### Drug therapy is indicated in:

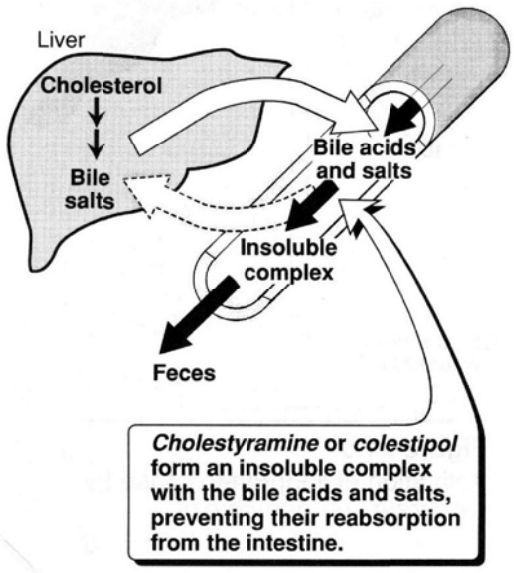
Failure of non-drug therapy.

Primary (hereditary) hyperlipidemia.

## Cholestyramine and colestipol

### Mechanism of action

They form **complexes** with bile acids in the intestine and ↓ enterohepatic absorption of bile salts and ↓ absorption of cholesterol.


Liver
Cholesterol
Bile salts
Bile acids and salts
Insoluble complex
Feces
*Cholestyramine* or *colestipol* form an insoluble complex with the bile acids and salts, preventing their reabsorption from the intestine.

### Therapeutic uses

- Hypercholesterolemia **(type IIa):** Bile acid sequestrants are effective in reducing plasma cholesterol (10%–20%) in patients with some normal LDL receptors.
- Diarrhea due to bile acid malabsorption.
- Pruritus due to obstructive jaundice.

### Adverse effects

- GIT upset (the most common): nausea, vomiting and **steatorrhea** (due to ↓ fat absorption).
- ↓ absorption of fat-soluble vitamins.
- ↓ absorption of anionic drugs e.g. digitalis and warfarin.

## Ezetimibe

### Mechansism of action

Ezetimibe is a selective inhibitor of intestinal cholesterol absorption. It is effective even in the absence of dietary cholesterol because it inhibits reabsorption of cholesterol excreted in the bile.

**Therapeutic uses**

Hypercholesterolemia: ezetimibe is synergistic with HMG-CoA reductase inhibitors, producing decrease of 25% in LDL cholesterol.

**Adverse effects**

Reversible hepatic dysfunction: liver function tests should be done at regular intervals.

## HMG-CoA reductase inhibitors (Statins)

**(Lovastatin, Pravastatin, Mevastatin, Atorvastatin)**

**Mechanism of action**

Competitive **inhibition of hydroxy-methyl-glutaryl coenzyme-A** (HMG-CoA) **reductase** → ↓ **cholesterol synthesis** and ↑ hepatic uptake of LDL.

**N.B.**

Statins should be taken at night as this is when the majority of cholesterol synthesis takes place. This is especially true for simvastatin which has a shorter half-life.

**Therapeutic uses**

- Hypercholesterolemia **(type II).**
- With other drugs for combined hyperlipidemia**.**

**Adverse effects**

**H** : **Hepatic dysfunction** leading to elevation of serum transaminases. Therapy should be stopped if liver enzymes rise > 3-folds the upper normal value.

**M** : **Myopathy, myositis** and **rhabdomyolysis** in both **skeletal** and **cardiac** muscle leading to ↑ of *creatine phosphokinase (CPK)* enzyme.

**G** : **GIT upsets:** nausea, vomiting, anorexia (the most common).

**Co-A** : **Cataract** (lenticular **O**pacity) in middle-**A**ged individuals.

**Reductase** : **R**enal dysfunction (especially with lovastatin).

## Fibric acid derivatives (Fibrates)

**(Clofibrate, Fenofibrate, Bezafibrate, Gemfibrozil)**

**Mechanism of action**

Fibrates act on **nuclear receptors** called *peroxisome proliferator activated receptors-α (PPAR-α)* leading to ↑ synthesis of **lipoprotein lipase** → ↑ peripheral catabolism of **VLDL** and **chylomicrons (TGs).**

**Therapeutic uses:**

- Hypertriglyceridemia **(types IIb, III, IV and V).**
- Fenofibrate has **antidiuretic action** in individuals with mild to moderate diabetes insipidus.

### Adverse effects

- **GIT upsets:** nausea, vomiting (the most common).
- Increase formation of **cholesterol gallstones**.
- **Hepatic dysfunction** and elevation of serum transaminases.
- Fibrates increase the **risk of myopathy** if used in combination with **statins**.
- Skin **rash** and dermatologic reactions.

## Nicotinic acid (Niacin; vitamin B3)

### Mechanism of action

- Niacin (but not nicotinamide) **inhibits lipolysis** in adipose tissue and inhibits **fatty acid synthesis** by the liver → ↓ hepatic **VLDL** and **LDL** synthesis.
- This is distinct from the role of niacin as a vitamin, in which it is converted to nicotinamide and is used for the biosynthesis of the cofactors NAD and NADP.

### Therapeutic uses

In combination with other drugs for **all types** of hyperlipidemia (**except type I** which is mainly treated by diet control).

### Adverse effects

- **Skin flushing** and **burning** sensation (the most common). It is harmless effect mediated by PGs and histamine release and can be diminished by taking aspirin 30 minutes before taking nicotinic acid.
- Gastric irritation (the drug should be avoided in peptic ulcer).
- Hyperglycemia, hyperuricemia, and reversible increase in serum transaminases.

### Summary

| | Effect on LDL | Effect on HDL | Effect on TGs |
|---|---|---|---|
| **Bile acid-binding resins** | ↓↓↓ | ↑ | ---- |
| **Reductase inhibitors** | ↓↓↓ | ↑ | ↓ |
| **Fibrates** | ↓ | ↑ | ↓↓↓ |
| **Niacin** | ↓ | ↑↑↑ | ↓↓ |

### Treatment with drug combinations

| | |
|---|---|
| **Hypercholesterolemia** | Cholestyramine + Reductase inhibitors |
| **Hypertriglyceridemia** | Niacin + Fibrates |
| **Familial combined hyperlipidemia** | Cholestyramine + Fibrates.<br>Cholestyramine + Niacin.<br>Statins + Fibrates *(this combination may ↑ risk of myopathy).* |

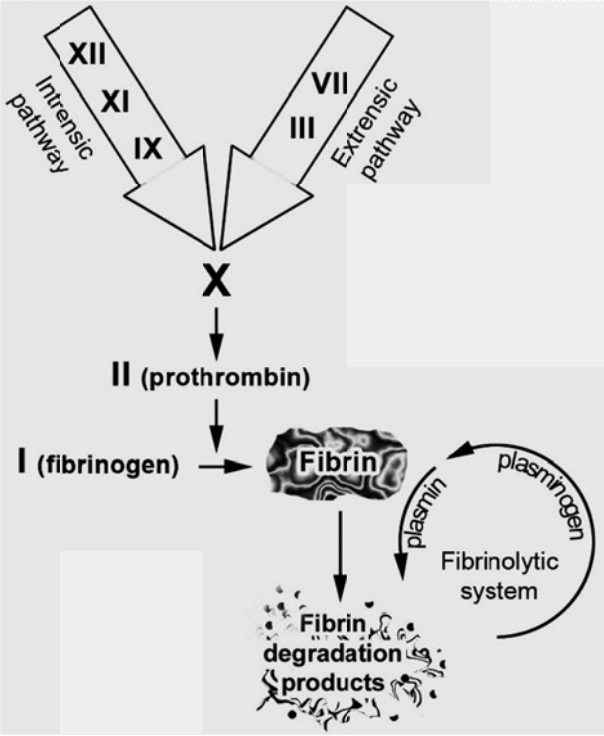
# Part 2: Drugs affecting hemostasis

## Basic information

**Hemostasis** is the spontaneous arrest of bleeding from damaged blood vessel.

## The coagulation system:

It consists of a number of plasma proteins (factors). Each factor activates another till activation of fibrinogen to form fibrin.
Activation cascade is done through 2 systems: the **intrinsic system** (can be monitored by the activated partial throboplastin time "APTT") and the **extrinsic system** (can be monitored by prothrombin time).




### Prevention of clotting:

- Plasma contains a number of proteins that normally prevent clotting through inhibition of clotting factors (e.g. **antithrombin III).**
- **Heparin** activates antithrombin III thus inhibits activation of factors IX, **X**, XI, and XII.
- **Oral anticoagulants** inhibit synthesis of clotting factors by the liver.

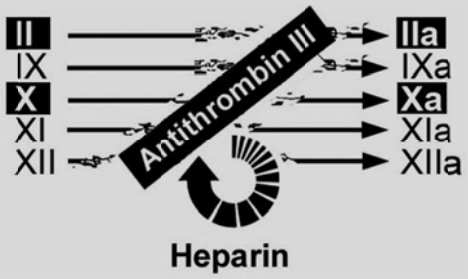
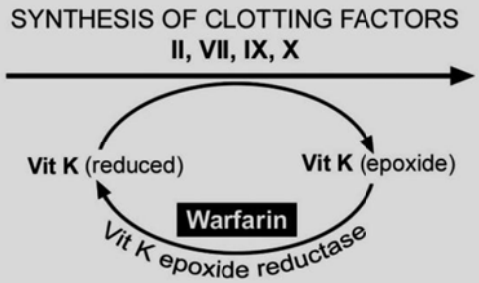
### Dissolution of blood clots:

- There are other plasma proteins that can dissolve blood clots (i.e. *fibrinolytic system* e.g. **plasmin)**.
- There are some drugs that activate plasminogen to form the active plasmin and thus enhance fibrinolysis (e.g. **streptokinase, urokinase, etc.).**
- **Aminocaproic acid** is an inhibitor of fibrinolysis.

## Drugs can affect hemostasis and thrombosis through:

- By modifying the integrity of the **vessel wall.**
- By modifying **blood coagulation** (clot formation).
- By modifying **platelet** adhesion and activation.
- By modifying **fibrinolysis.**

## DRUGS THAT PREVENT COAGULATION (ANTICOAGULANTS)

| | Heparin | Warfarin (Oral anticoagulant) |
|---|---|---|
| **Source & chemistry** | Natural sulfated polysaccharide present in mast cells & carries **–ve** charge<br>Commercial preparations are derived from bovine lung or porcine intestinal extracts | Synthetic cuomarin compound |
| **Absorption**<br><br>**Distribtion** | ▪ **No** because it precipitates by gastric HCl.<br>▪ Can**not** cross BBB or placenta. | ▪ **Good** (bioavailability is 100%).<br>▪ Can cross BBB and placenta. |
| **Mechanism of action** | ▪ Its action depends on the presence of a natural clotting inhibitor called heparin cofactor **(antithrombin III)** in plasma.<br>▪ Small quantities of heparin can activate antithrombin III leading to inhibition of several clotting factors especially factor X & thrombin (factor II).<br>  | ▪ Warfarin inhibits **vitamin K epoxide reductase enzyme** in the **liver** leading to inhibition of formation of the active form of vitamin K → ↓ synthesis of vitamin K-dependent clotting factors **(II, VII, IX,** and **X)**.<br>▪ The action of warfarin could be antagonized by vitamin K.<br>  |
| **Onset and duration** | **Immediate** and **short** (2-4 hrs). | **Delayed** for 8-12 hrs *(time needed for depletion of clotting factors & vit K)* and **long** (3-7 d) |
| **Pharmacol effects** | ▪ Anticoagulant **in vivo** & **in vitro**<br>▪ Stimulates *lipoprotein lipase* → ↓↓ serum triglycerides (TGs). | Anticoagulant **in vivo** only. |
| **Therapeutic uses** | ▪ **Treatment of established thrombosis:** heparin is given parenteral 5000-10,000 U **i.v.** then 5000 U **s.c.**/8h to maintain blood coagulation 2-3 times as normal and prevent further | Warfarin is given oral 2-10 mg/day for **prevention and treatment of:**<br>– Deep vein thrombosis **(DVT)**<br>– Postoperative thrombosis.<br>– Cerebral venous thrombosis. |

| | | |
|---|---|---|
| | extension of the thrombus.<br>▪ **Prevention of thrombosis:** 5000 U **s.c.**/8-12 hrs. | – Coronary thrombosis: treatment continued for several years.<br>– Acute arterial & pulmonary **embolism**: anticoagulation is initiated by heparin and maintained by warfarin.<br>– **AF** and **artificial** heart valves |
| **Monitoring of therapy** | By **activated partial thromboplastin time (APTT).** It must be kept 2-3 times as the normal value. | By **prothrombin time (PT) or International Normalized Ratio (INR). I**t is the ratio of the PT in the patient to that of normal person. It must be kept 2-3 times as the normal value. |
| **Adverse effects** | ▪ **Bleeding is the most common and dangerous SE** (e.g. hematuria & major organ bleeding). It could be treated by the following:<br>(a) Immediate stopping of the drug.<br>(b) Fresh frozen plasma (FFP): to provide fresh clotting factors.<br>**(c) Protamine sulfate (Protam):**<br>– Protamine carries **+ve** charge that combines with heparin (carries **-ve** charge) to form stable complex.<br>– **1 mg** of protamine can bind to **100 U** of heparin. | **(c) Vitamin $K_1$:** 10 mg slowly i.v. or i.m. to enhance synthesis of clotting factors. |
| | ▪ **Hematoma** if given **IM** (so, contraindicated to give it IM).<br>▪ **Thrombocytopenia:** immune-mediated reaction due to formation of antibodies that can bind to platelets. Platelet count should be performed regularly<br>▪ **Osteoporosis** and spontaneous fractures on long-term therapy<br>▪ **Alopecia and dermatitis:** rare and transient. | ▪ **Hemorrhagic skin necrosis**: when starting warfarin, biosynthesis of protein C is reduced leading to temporary procoagulant state. This can lead to hemorrhagic infarction of skin, breast, intestine and fatty tissue. normally avoided by concurent heparin administration.<br>▪ **Teratogenicity:** abnormal bone formation in early pregnancy *(fetal warfarin syndrome).*<br>▪ **CNS Hemorrhage** in the fetus if given in late pregnancy.<br>▪ **Sudden withdrawal** may lead to thrombotic catastrophes. |

## Low-molecular-weight heparins (LMWH) (Enoxaparin – Dalteparin)

- **Standard (unfractionated) heparin** is a mixture of different molecular weight fractions (MW 3000-30,000 Da) that can affect more than one coagulation factor and produce thrombocytopenia (↑ risk of bleeding).
- **LMWH** has a MW less than 8000 Da that makes it **specific for factor X** with minimal effects on platelets and other clotting factors.

Hemorrhagic skin necrosis caused by warfarin

| | Unfractionated heparin | LMWH |
|---|---|---|
| Molecular weight range | Wide (ranges from 3000 to 30,000 Da) | Less than 8000 Da |
| Anti-factor Xa activity | Less specific | More specific |
| Non-specific binding to vascular endothelium and plasma proteins | High | Low |
| Bioavailability after s.c. injection | Low *(due to binding to s.c. tissue)* | High |
| Half-life | Short (given 3 times/d) | Long (given once/d) |
| Thrombocytopenia | Common (10%) | Less common (<2%) |
| Risk of bleeding | High | Low |
| Lab monitoring | APTT (Essential) | Anti-factor Xa levels (May be unnecessary) |

### Synthetic factor Xa inhibitors

| | |
|---|---|
| **Fondaparinux** | – Synthetic polysaccharide that have the same mechanism like LMWH (i.e. selective inhibitor of factor Xa).<br>– It is given by **s.c.** injection **once daily** (has long t½). |

### Direct thrombin inhibitors (DTIs)

| | |
|---|---|
| **Bivalirudin** | – It is a synthetic **hirudin analogue** (hirudin is a direct thrombin inhibitor peptide present in the saliva of medicinal **leech)**.<br>– Bivalirudin is a reversible and short-acting DTI. It is given **i.v.** |

| | |
|---|---|
| | – It is approved as alternative to heparin to treat patients with heparin-induced thrombocytopenia.<br>– **Bleeding** is the major side effect. |
| **Argatroban** | – Synthetic compound that binds reversibly to **thrombin**.<br>– It can be used as alternative to heparin to treat patients with heparin-induced thrombocytopenia.<br>– It is given **i.v.** and has immediate onset of action. |
| **Dabigatran** | – It is the first **oral** DTI approved by the FDA in 2010.<br>– It was found superior to warfarin in preventing the risk of stroke and systemic embolism in susceptible patients. |

**Use of anticoagulants during pregnancy**

- Pregnancy is a hypercoagulable state due to increase levels of coagulation factors and venous stasis. Pegnancy increases the risk of venous thrombosis and pulmonary embolism.
- The use of warfarin in the first trimester is associated with birth defects (5%), while its use near fullterm increases the risk of fetal hemorrhage.
- Neither UFH nor LMWH cross the placenta; therefore, do not cause fetal bleeding or teratogenicity, but they can reduce bone mass density and cause **osteoporosis** if used throught pregnancy.
- Anticoagulation is recommended in most pregnant patients with a mechanical heart valve. The American College of Chest Physicians (ACCP) recommends the use LMWH until 13 weeks' gestation, THEN change to warfarin until the patient is close to delivery (34 weeks), and THEN restart LMWH. Long-term anticoagulants should be resumed postpartum.

**Contraindications of anticoagulant therapy**

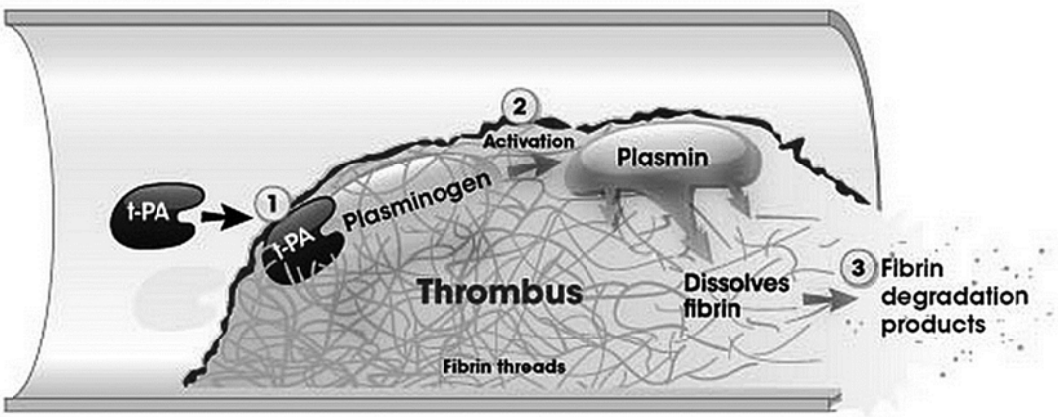
| | |
|---|---|
| **Hematological:** | – Hemorrhagic blood diseases e.g. hemophilia & thrombocytopenia. |
| **Neurological:** | – **R**ecent hemorrhagic stroke within 3 weeks.<br>– **R**ecent brain or eye surgery. |
| **CVS:** | – **S**ubacute bacterial endocarditis (SBE).<br>– Uncontrolled hypertension (→ risk of cerebral bleeding). |
| **GIT:** | – **A**ctive PU, esophageal varices, and hemorrhagic pancreatitis<br>– **A**ctive inflammatory bowel disease (ulcerative colitis). |
| **Liver:** | – Liver failure (this patient has bleeding tendency) |
| **Renal:** | – Renal failure. |
| **Gynecological:** | – Threatened abortion.<br>– Warfarin is not given in the first timester. |

**Drug interactions of oral anticoagulants (warfarin)**

| Drugs that potentiate warfarin | Drugs that inhibit warfarin |
|---|---|
| ▪ **Microsomal enzyme inhibitors** (e.g. cimetidine, chloramphenicol) ↓ metabolism of warfarin.<br>▪ **Oral antibiotics:** ↓ vit K synthesis by killing the gut flora<br>▪ **Liquid paraffin:** ↓ vit K absorption<br>▪ **NSAIDs:** displace warfarin from pp. | ▪ **Microsomal enzyme inducers** (e.g. phenobarbital, rifampin) ↑ metabolism of warfarin.<br>▪ **Oral contraceptives** and **vit K**. ↑ synthesis of clotting factors<br>▪ **Aluminum hydroxide:** ↓ warfarin absorption |

## FIBRINOLYTIC (THROMBOLYTIC) DRUGS

- Normally, when a fibrin clot is formed, **plasminogen** gets in contact with this clot and becomes activated into **plasmin** by the help of naturally occurring **tissue plasminogen activators (t-PAs)**. Plasmin causes lysis of the clot.
- These endogenous activators preferentially activate plasminogen that is bound to fibrin, which (in theory) confines fibrinolysis to the formed thrombus and avoids systemic activation.
- Fibrinolytic drugs cause rapid activation of plasminogen to form plasmin, but unfortunately, they may activate **both** fibrin-bound plasminogen and circulating plasminogen thus, both protective hemostatic thrombi and pathogenic thromboemboli are broken down (→ risk of bleeding).




(1) Recombinant t-PA (alteplase) binds to fibrin in thrombus (2) converts entrapped plasminogen to plasmin that (3) initiates local fibrinolysis.

### Streptokinase

- Streptokinase is a protein (not an enzyme) that is isolated from streptococci; it activates plasminogen into plasmin non-enzymatically.
- It may be antigenic (causes allergy) in some people.

### Urokinase

- Urokinase is a protease originally isolated from urine; the drug is now prepared in recombinant form from cultured kidney cells.
- It is less antigenic than streptokinase.

Streptokinase and urokinase act on both circulating plasminogen and fibrin-bound plasminogen causing a generalized fibrinolytic state (bleeding).

### Recombinant tissue plasminogen activators (t-PAs): (Alteplase, reteplase, and tenecteplase)

- They are recombinant human proteins produced in cultured cells.
- They are **most specific** to fibrin-bound plasminogen; local activation of plasmin at the thrombus site reduces the incidence of systemic bleeding.
- **Reteplase** and **tenecteplase** have long half-life. The long half-life permits administration as a bolus i.v. injection rather than by continuous infusion. (two injections i.v. separated by 30 minutes for **reteplase**, one single i.v. injection for **tenecteplase**).

### Therapeutic uses of thrombolytic drugs

- They are given by **i.v. route** in cases of acute **myocardial infarction**, ischemic stroke, pulmonary embolism, and arterial thrombosis.
- In cases of acute MI, they should be given within **12 h** of onset. The maximum benefit is obtained if treatment is given within **90** minutes of the onset of pain.
- Before thrombolysis, care should be taken to ensure there is no liability for bleeding in a critical site e.g. retina, CNS, etc.

### Adverse effects of thrombolytic drugs

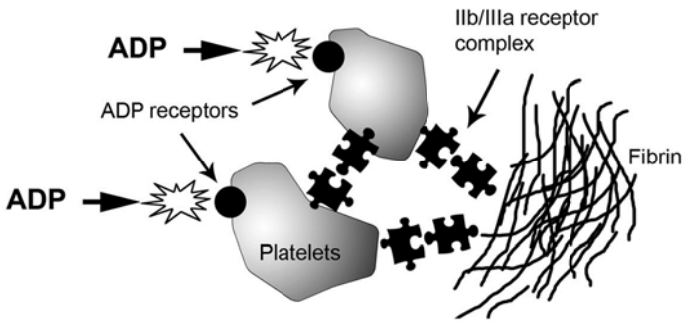
- **Systemic bleeding** is the major adverse effect. The risk is high with streptokinase and low with the recent recombinant tissue plasminogen activators.
- Streptokinase can cause **allergy, fever**, and **hypotension** during i.v. infusion.

## ANTIPLATELET (ANTITHROMBOTIC) DRUGS

### Aspirin

- Aspirin inhibit platelet aggregation by:
  - Irreversible inhibition of COX enzyme → ↓ $TXA_2$ → ↓ platelet *aggregation.*
  - Irreversible acetylation of platelet cell membranes → ↓ platelet *adhesions.*
  - Decrease platelet ADP synthesis → decrease platelet *accumulation.*
- At higher doses (> 325 mg/day), aspirin may decrease endothelial synthesis of PGI2, which inhibits platelet activity. Low doses (75-150 mg/day) ↓ synthesis of platelet TXA2 more than PGI2 in endothelial cells and avoid this effect.
- Other NSAIDs **do not have** comparable antithrombotic activity.

**Blockers of platelet ADP receptors:**
**(Ticlopedine, clopidogrel, prasugrel)**




- These drugs **irreversibly** inhibit the binding of **ADP** to its receptors on platelets and, thereby, inhibit the activation of the **glycoprotein IIb/IIIa** receptors required for platelets to bind to fibrinogen and to each other.
- **Clopidogrel** is approved for prophylaxis of thrombosis in both cerebrovascular and cardiovascular disease (e.g. coronary artery disease, coronary angioplasty, peripheral vascular disease, etc.). The maintenance dose is 75 mg/d orally.
- Clopidogrel is a **prodrug**, and its therapeutic efficacy relies entirely on its active metabolite. Some people have genetic deficiency in the enzymes that metabolize clopidogrel; they are called "**poor metabolizers**", and cannot benefit from this drug.
- Ticlopedine has been largely replaced by clopedogrel because of serious adverse effects (neutropenia and **bleeding**). Clopidogrel has **fewer** incidence of these effects.

**Blockers of platelet glycoprotein IIb/IIIa receptors:**
**(Abciximab, eptifibatide, tirofiban)**

- Activation of this receptor complex is the "final common pathway" for platelet aggregation and binding with fibrinogen. Persons lacking this receptor have a bleeding disorder called Glanzmann's thrombasthenia.
- **Abciximab** is the Fab fragment of a monoclonal antibody that binds to gpIIb/IIIa and blocks binding of platelets to fibrinogen.
- **Eptifibatide** is a small synthetic peptide that competitively blocks gpIIb/IIIa receptor.
- **Tirofiban** is a peptide of low MW that binds to the gpIIb/IIIa receptor.
- These drugs have been approved for use in patients undergoing percutaneous coronary intervention, for unstable angina, and for post-MI.

**Dipyridamole**

- Dipyridamole **inhibits phosphodiesterase (PDE) enzyme** → ↑ cGMP → VD and inhibition of platelet activity. It also **inhibits uptake of adenosine** into platelets and RBCs leading to extracellular accumulation and prolongation of its action.
- The use of dipyridamole as an antithrombotic agent is limited to prophylaxis (combined with warfarin) in patients with **prosthetic** (mechanical) **heart valves.**

## DRUGS USED IN BLEEDING DISORDERS (HEMOSTATIC AGENTS)

### Systemic agents

- **Vitamin K:** essential for synthesis of factors II, VII, IX, X by the liver.
- **Vitamin C** and **rutin:** preserve the integrity of the vascular wall.
- **Fresh blood or plasma transfusion:** as sources of coagulation factors.
- **Plasma fractions:**
  - Thromboplastin (factor III): prepared from mammalian tissues.
  - Antihemophilic globulin (factor VIII): given in hemophilia A.
- **Calcium (factor IV):** as a coagulation factor.
- **Aminocaproic acid** and **tranexamic acid:** inhibitors of fibrinolytic system.
- **Ethamsylate (Dicynone):** given i.m. to reduce capillary bleeding.

### Local agents

- **Physical methods:** application of pressure, cooling or heat coagulation.
- **Vasoconstrictor drugs:** e.g. adrenaline nasal pack in epistaxis.
- **Astringents:** drugs which precipitate surface proteins e.g. alum sulphate.
- **Thrombin** and **thromboplastin:** applied on the bleeding surface as powders.
- **Fibrin and fibrinogen:** available as dried sheets and used in surgery.
- **Oxidized cellulose:** it forms an adhesive mass on the bleeding surface.
- **Sclerosing agents:** chemicals that cause thrombosis in veins and permanent obliteration, e.g. ethanolamine oleate (given i.v. for varicose veins).

### Vitamin K

- **Vitamin K1 (phytomenadione)** is a naturally occurring **fat-soluble** vitamin present in green vegetables. It is available clinically in oral and parenteral forms.
- **Vitamin K2** is synthesized by intestinal bacteria.
- Both vitamins K1 and K2 require **bile** salts for absorption from the intestine.

**Mechanism of action:** Vitamin K is required for posttranslational modification of clotting factors II, VII, IX, and X by liver cells.

#### Therapeutic uses

- To reverse bleeding episodes caused by **overdose of warfarin, salicylates**, and oral hypoglycemic drugs.
- To correct **vitamin deficiency** caused by dietary deficiency, or in patients receiving oral antibiotics.
- To prevent **hypothrombinemia of the newborn**: all newborns should routinely receive 1–2 mg of vitamin K directly after birth (especially in premature infants).

**Adverse effects:** parenteral vitamin K1 is dissolved in **oil**; rapid i.v. administration can cause dyspnea, chest pain, or even death.

**N.B. severe hepatic failure** is associated with bleeding tendency (due to reduced synthesis of clotting factors) that **does not** respond to vitamin K.

## Plasma fractions

- Deficiencies in plasma coagulation factors can cause bleeding. Spontaneous bleeding occurs when factor activity is **less than 5–10% of normal**. Factor VIII deficiency (classic hemophilia, or hemophilia A) and factor IX deficiency (Christmas disease, or hemophilia B) account for the most common heritable coagulation defects.
- Plasma protein preparations are available for treatment of these disorders. They are administered **i.v.**
- Plasma fractions are frequently prepared from **blood** or **plasma** pooled from multiple individuals; thus, they are associated with high risk of exposure to **infection** (hepatitis and HIV). For this reason, recombinant preparations are recommended whenever possible.

**Hemophilia**

Genetic deficiency of factor VIII (hemophilia A) or IX (hemophilia B).

**Manifestations:** bleeding on minor trauma.

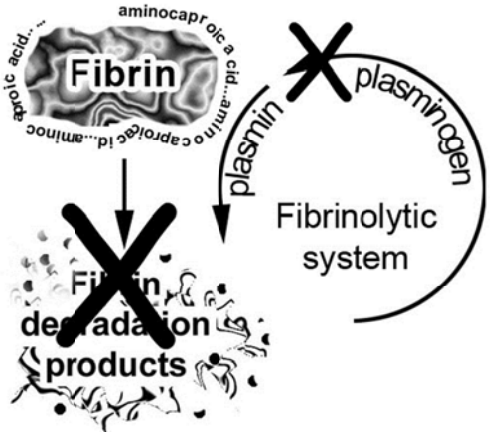
**Treatment:**
1. **Plasma fractions:** antihemophilic globulin (factor VIII) in hemophilia A and Christmas factor (factor IX) in hemophilia B.
2. **Desmopressin** (intranasal): can ↑ factor VIII activity (but not factor IX).
3. **Tranexamic acid:** help to stabilize blood clots in both diseases.

## Inhibitors of fibrinolysis:
## (Aminocaproic acid and tranexamic acid)

**Aminocaproic acid** is a synthetic agent that competitively inhibits plasminogen activation. **Tranexamic acid** is more potent analogue of aminocaproic acid.

### Therapeutic uses

- To prevent **bleeding** from tissues rich in plasminogen activators e.g. lung, prostatic surgery, menorrhagia, and ocular trauma.
- Prophylaxis for rebleeding from **intracranial aneurysm**.
- As adjunctive therapy in **hemophilia**.
- To stop bleeding caused by **toxicity of fibrinolytic drugs**.



## DRUGS AFFECTING BLOOD VISCOSITY

### Pentoxifylline

- **Pentoxifylline** is a synthetic methylxanthine structurally similar to caffeine.
- Pentoxifylline appears to inhibit RBCs **phosphodiesterase (PDE)** → ↑ **RBC** membrane **flexibility** and ↓ blood viscosity (rheologic modifier).
- It is approved for use to improve microvascular circulation in patients with **intermittent claudication**, diabetic angiopathy, chronic leg ulcers, and peripheral vascular disease.

# Part 3: Drugs used in the treatment of anemias

Anemia is defined as a low hemoglobin (Hb) concentration due to **reduced production** or **increased loss** of RBC. The WHO defines anemia as Hb <13 g/dL in men or <12 g/dL in women.

## Iron deficiency anemia (hypochromic microcytic anemia)

- Iron deficiency is the most common cause of anemia.
- The total amount of transferrin determines the **total iron-binding capacity** (TIBC) of plasma.
- **Transferrin saturation** (i.e. plasma iron/TIBC) is normally 20–50% and provides a useful index of iron status.
- In iron-deficiency states, there is ↓ in plasma iron and ↑ in TIBC, so transferrin saturation is **< 20%.** The opposite occurs in hemochromatosis.

### Iron

- **Absorption:**
  - Iron is absorbed from upper small intestine in the ferrous state (Fe2+) more than in the ferric state (Fe3+). About 10% of dietary iron is absorbed.
  - Factors that ↑ absorption: pregnancy & growing infants, gastric HCl and vit C.
  - Factors that ↓ absorption:
    - Malabsorption syndromes: e.g. celiac disease.
    - *Antacids:* form insoluble complexes with iron.
    - *Tannic acid* (strong tea): precipitates iron
    - *Tetracyclines:* chelate iron.
- **Transport:** in plasma via **transferrin** and stored in the reticulo-endothelial system and bone marrow as **ferritin**.

**N.B.**

**Hepcidin** is a protein synthesized by the liver. It **decreases** iron absorption by the intestine, and it may contribute to the anemia of chronic diseases.

- **Excretion:** There is no active mechanism for excretion of iron. Small amounts are excreted through stool, urine, and sweat. The main regulation of iron level in the body is done at the level of absorption.

**Causes of iron deficiency anemia (= Indications of iron therapy)**

- **Deficient intake:** e.g. poor diet or malabsorption syndrome.
- **Increased demand:** e.g. in **p**regnancy and **p**remature babies (iron & folic acid should be given to pregnant women from the 4th month).
- **Excessive blood loss**.

**Preparations of iron**

- **Oral iron:**
  - Many oral iron preparations are available (*Ferrous sulfate*, *ferrous gluconate, & ferrous fumarate)* which are are **effective** and recommended for most patients. Vitamin C may be given with iron to improve absorption.
  - The Hb usually reaches normal levels within **1-2 months** but treatment should be continued for **3-6 months** to replenish iron stores.

- **Parenteral iron:**

  **Indications:**
  - Inability to tolerate or absorb oral iron.
  - Severe anemia or extensive blood loss cannot be corrected by oral iron.

  **Administration:**
  - *Iron dextran or iron carboxymaltose* **is** given by slow i.v. infusion as a 1000 mg diluted in 500 ml saline over 1-2 hours. The initial 25 ml should be infused slowly (as a test dose) and the patient should be observed for allergic reactions.
  - Other parenteral preparations should be administered according to product labeling information.

**Adverse effects of iron**

- **Oral iron: GIT upset** (most common)**:** nausea, epigastric pain, abdominal cramps, constipation or diarrhea. These effects can be minimized by taking iron after meals.

- **Parenteral iron:**
  - Local pain and tissue staining with i.m. injection.
  - Anaphylactoid (allergic) reaction in 3% of patients. True anaphylaxis is very rare.
  - Lymphadenopathy.

## Iron toxicity

- **Acute iron toxicity:**

  **Causes:** more frequent in children due to accidental ingestion of iron tablets.

  **Manifestations:**
  - Vomiting, hematemesis and bloody diarrhea.
  - Metabolic acidosis, shock, coma & death.

  **Treatment:**
  - Gastric lavage by phosphate or carbonate solutions to form insoluble complexes.
  - **Desferrioxamine** (**Desferal**; iron chelating compound): 1-2 gm i.m. to chelate systemically absorbed iron. It can cause hypersensitivity reaction.
  - Supportive treatment for GIT bleeding, metabolic acidosis, and shock.

- **Chronic iron toxicity:**

  **Causes:**
  - Excessive iron absorption: e.g. in **hemochromatosis** (autosomal recessive disorder characterized by ↑ iron absorption; transferrin saturation is >50%)
  - Excessive blood transfusion: e.g. in thalassemia major.

  **Manifestations:** excess iron is deposited in the liver, pancreas and skin.

  **Treatment:**
  - Intermittent phlebotomy is the treatment of choice: one unit of blood is removed every one week until the excess iron is removed.
  - Periodic desferrioxamine i.m. when phlebotomy cannot be performed e.g. in patients with thalassemia major.

## Red cell deficiency anemia (Anemia of chronic renal failure)

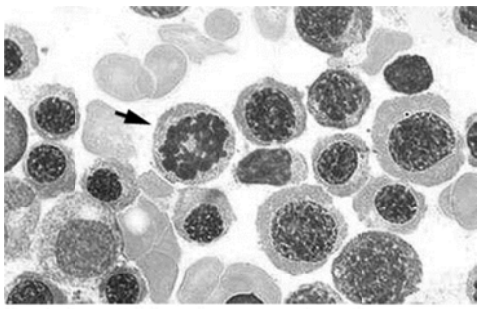
- **Erythropoietin (EPO)** is a glycoprotein secreted by interstitial cells of the renal cortex (90%) and 10% by the liver. It is essential for normal reticulocyte production. Patients with chronic renal failure develop **red cell deficiency anemia** due to deficiency of EPO.
- Recombinant human EPO is available **(epoetin alfa,** and **darbepoetin)** for treatment of the following anemias:
  - Anemia of chronic renal failure.
  - Anemia due to bone marrow suppression e.g. cancer chemotherapy or zidoviodin (AZT) therapy.
  - Anemia of multiple myeloma and rheumatoid arthritis.
- EPO is given s.c. injection once weekly to target Hb level between **10-12 gm/dl**.

**Adverse effects**

- **Hypertension** and increased blood viscosity (due to ↑ RBC mass) leading to thrombotic complications especially when **Hb is > 12 gm/dl**.
- **Seizures** and headache probably caused by rapid expansion of blood volume.
- **Iron deficiency** due to rapid ↑ in RBC mass, so **parenteral iron** should be given with EPO (**N.B.** in renal failure, oral iron is not effective due to poor absorption in such case).

## Vitamin deficiency (megaloblastic) anemias

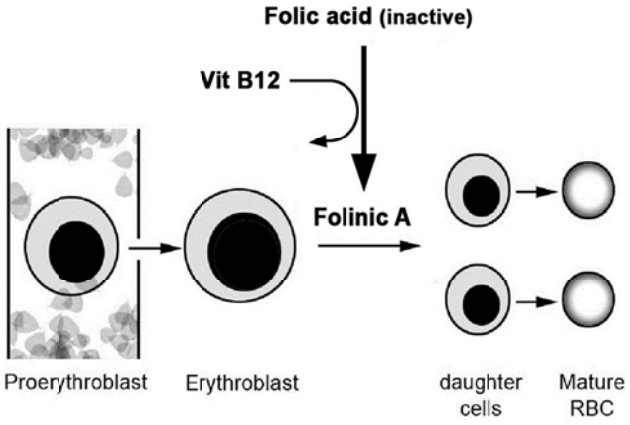
- Megaloblastic (macrocytic) anemia results from failure of DNA synthesis during RBCs development. Failure of DNA synthesis leads to continuing cell growth without division, which presents as nonfunctioning macrocytosis.
- The defect in red cell DNA synthesis is most often due to deficiency of vitamin B12 and /or folic acid. Vitamin B12 is needed as a co-factor for conversion of dihydrofolic acid into the **active form** (folinic acid) which is important for DNA synthesis.



Peripheral blood smear showing hypersegmented neutrophils, characteristic of megaloblastic anemia.

### Vitamin $B_{12}$ (cyanocobolamine)

- **Vitamin B12** is essential for normal **DNA** synthesis, which is most apparent in tissues that are actively dividing, such as the GI tract and erythroid precursors.
- Vitamin B12 is absorbed from the distal ileum after binding to the intrinsic factor.




### Deficiency of vitamin $B_{12}$

- **Blood:** megaloblastic anemia.
- **GIT:** sore tongue and abnormal GIT epithelium.
- **CNS (Subacute Combined Degeneration):** degeneration of the brain, spinal cord and demyelination of nerve sheath.

**Pernicious anemia**

Atrophy of the gastric mucosa that becomes unable to secrete intrinsic factor or HCl → chronic vit B12 deficiency.

**Therapeutic uses**

- **Megaloblastic and pernicious anemia:**
  - If there is no neurological manifestations, it is given as 1 mg i.m. 3 times/week for 2 weeks, then once every 3 months.
  - Improvement in Hb concentration is apparent in 7 days and normalizes in 1–2 months.
  - Pernicious anemia requires life-long treatment.
- Peripheral neuropathy especially **diabetic neuropathy**.
- Hydroxocobalamin (variant of vit $B_{12}$) can be used in **cyanide poisoning**. It acquires the CN ions and is converted into cyanocobolamine.

## Folic acid (vitamin B9; leucovorin)

Folic acid is composed of three subunits: pteridine, para-aminobenzoic acid (PABA), and one to five glutamic acid residues. Absorbed folic acid from diet requires reduction by *dihydrofolate reductase* to the active form **tetrahydrofolate**.

**Deficiency of folic acid**

- **Megaloblastic anemia** is more common with folic acid deficiency than vitamin B12 deficiecncy. It occurs after 4 months of folic acid deficiency.
- Folic acid deficiency during pregnancy leads to **neural tube defect**.

**Therapeutic uses**

- **Megaloblastic anemia:**

  In megaloblastic anemia there is deficiency of **vit $B_{12}$** or **folic acid.** If the patient has combined deficiency of both agents, it is necessary to treat vitamin B12 deficiency first because administration of folic acid alone leads to utilization of all vitamin B12 stored in tissues for developing red cells; so, anemia would be partially corrected but neurogenic symptoms are aggravated *(subacute combined degeneration)*

- **Pregnancy:** folate requirement is increased from 400μg to 800μg/day to prevent **fetal neural tube defect (spina bifida).**
- To prevent toxicity of **antifolate drugs:** see box.
- Malabsorption syndrome.

**Antifolate drugs**

| | |
|---|---|
| Trimethoprim<br>Pyrimethamine<br>Methotrexate | ↓ Folinic acid synthesis |
| Oral contraceptives | ↓ Folic acid absorption |
| Phenytoin<br>Phenobarbital | ↑ Folic acid metabolism |

## Hemopoietic growth factors

- **Erythropoietin (EPO):** see before.

- **Granulocyte/macrophage colony stimulating factor (GM-CSF)**

– GM-CSF is a recombinant protein expressed in yeasts. Ilts principal action is to stimulate myelopoiesis in granulocyte–macrophage pathways as well as megakaryocytic and erythroid progenitor cells.

– **Uses:**
  – It is given **i.v.** in cases of neutropenia and aplastic anemia.
  – To stimulate stem cells after bone marrow transplantation.

– **Adverse effects:**
  – **F**ever & **F**atigue
  – Arthralgia *(bone pain)* & myalgia *(muscle pain)*.
  – **Capillary leak syndrome:** edema, pleural and pericardial effusion.

- **Granulocyte colony stimulating factor (G-CSF; Filgrastim)**

– G-CSF stimulates maturation of immature **neutrophils**.
– **Uses:** Neutropenia due to cancer chemotherapy.
– **Adverse effects:** similar to GM-CSF

- **Megakaryocyte (platelet) growth factor**

– **Interleukin-11 (IL-11)** is a protein produced by fibroblasts and stromal cells in the bone marrow. It acts on specific cell receptors to stimulate growth of primitive **megakaryocytes** to form mature **platelets**.
– **Oprelvekin** is a recombinant IL-11 approved for treatment of thrombocytopenia.

## Drug-induced aplastic anemia (bone marrow depression)

- It is considered the most serious **drug-induced** hematologic effect because of the **high** mortality rate, (> 50% of cases). It is diagnosed by presence of **two** of the following criteria:
  – WBC count ≤ 3500/$mm^3$,
  – Platelet count ≤ 55,000/$mm^3$
  – Hb ≤ 10 g/dL

- There is fever and pharyngitis not responding to antibiotics, pallor, petechiae, and bleeding appear on the average about **5-6** weeks after the initiation of the offending agent.

**Mechanism of drug toxicity**

Damage to the hematopoietic stem cells due to:

- Direct, dose-dependent drug toxicity (the most common mechanism)
- Formation of toxic metabolites (idiosyncrasy).
- Immune reaction.

**Management**

- Stop the offending drug.
- Give fresh blood transfusion.
- Corticosteroids to inhibit the immune reaction.
- C-CSF or GM-CSF.
- Penicillin to combat infection.
- Stem cell transplantation in severe or resistant cases.

**Drugs associated with drug-induced aplastic anemia**

- Chloramphenicol
- Anti-cancer drugs
- Anti-thyroid drugs
- Carbamazepine
- Sulfonamides
- Interferone-alfa

Notes

Clinical
Pharmacology
Department

Mansoura Faculty of Medicine

## Review Questions

**Classify** hypolipidemic drugs. Mention the mechanism of action of each class.

**Mention the mechanism of action and adverse effects of each of the following:**

- HMG CoA reductase inhibitors (statins).
- Clopidogrel
- Erythropoietin
- Niacin

**Mention the mechanism of action and therapeutic uses of:**

- Vitamin K1
- Tranexamic acid
- Warfarin

**Mention the essential lines of the treatment of**:

- Iron toxicity
- Heparin toxicity
- Warfarin toxicity

**Give the reason:**

- vit B12 must be combined with folic acid during treatment of megaloblastic anemia.
- Parenteral iron should be given during erythropoietin therapy.

**Mention 3 differences between:**

- Streptokinase and alteplase (t-PA).
- Standard heparin and low molecular weight heparin.

Mention the mechanism and management of **drug-induced bone marrow depression.**

Mention the **drug-drug interactions of warfarin.**

**Of each of the following questions, select ONE BEST answer:**

**1. All of the following lipid-lowering drugs are correctly matched with their mechanism of action EXCEPT:**
A. Cholestyramine – bile acid binding resin
B. Niacin – inhibits lipolysis
C. Clofibrate – HMG-CoA reductase inhibitor
D. Gemfibrozil –activation of lipoprotein lipase
E. Lovastatin – inhibits cholesterol biosynthesis

**2. Niacin or nicotinic acid:**
A. Inhibits HMG-CoA reductase
B. Increases plasma levels of VLDL
C. Lowers triglycerides due to its action as a vitamin.
D. Should not be combined with a bile acid-binding resin
E. Inhibits the production of VLDL in the liver.

**3. Simvastatin, an HMG-CoA reductase inhibitor- All are true EXCEPT:**
A. Lowers low density lipoprotein (LDL) cholesterol
B. Is particularly useful in heterozygous familial hypercholesterolemia
C. Acts locally on HMG-CoA reductase in the intestine
D. May be associated with rhabdomyolysis
E. Is effective if prescribed with a bile acid binding resin.

**4. Absorption of iron:**
A. Is greater in anemic man than in normal one
B. Is decreased by ascorbic acid.
C. Is more efficient when it is in ferric form
D. Takes place mostly in the ileum.
E. Is enhanced by co-administration of desferroxamine

**5. In the treatment of iron deficiency anemia:**
A. Therapy with iron should last for 6 months to replenish iron stores
B. Parentral iron is usually preferred than oral iron
C. The patient is advised to take oral iron on an empty stomach.
D. Black stool is a strong indication for discontinuation of oral iron.
E. Metabolic alkalosis is the major feature of acute iron toxicity

**6. Vitamin B12:**
A. Is normally absorbed in the upper small intestine
B. Therapy by mouth is the first choice in pernicious anemia
C. Is good trial therapy in undiagnosed anemias
D. Its deficiency can lead to anemia and neurological symptoms
E. Is the first choice for the treatment of aplastic anemia.

**7. Recombinant human erythropoietin has been used for the treatment of:**
A. Aplastic anemia
B. Anemia associated with renal failure
C. Megaloblastic anemia
D. Sickle cell anemia
E. Thalassemias

**8. All of the following anticoagualnt drugs are correctly matched with their mechanism of action EXCEPT:**
A. Warfaine – inhibits synthesis of vitamin K-dependent clotting factors in the liver
B. Heparin – increases the activity of antithrombin III in plasma
C. Bivalirudin – selectively inhibits thrombin action
D. LMWH – selectively inhibit factor IX.
E. Fondaparinux – selectively inhibits factor X.

**9. The anticoagulant action of heparin can be effectively antagonized by:**
A. Vitamin C
B. Vitamin K
C. EDTA
D. Thromboplastin
E. Protamine

**10. All the following statements about vitamin K are correct EXCEPT:**
A. Is widely distributed in plants.
B. Requires bile for its absorption
C. Is necessary for the formation of factor IX in the liver.
D. Increases synthesis of prothrombin in patients with severe liver disease.
E. Deficiency may occur as a result of oral antibiotics.

**11. In thrombolytic therapy, one statement is NOT true:**
A. Streptokinase should be given within 6 hrs of coronary thrombosis.
B. Recombinant tissue plasminogen activator is superior to streptokinase
C. Streptokinase is easier to use than urokinase since it is non-antigenic
D. Bleeding remains the major side effects of all fibrinolytic drugs.
E. The complication of bleeding should be treated by tranexamic acid.

**12. The following statements about platelet activity are correct EXCEPT:**
A. Intact vascular endothelium does not attract platelets because it synthesizes PGI2.
B. TXA2 is synthesized mainly by platelets.
C. Dipyridamole reduces platelet activity by increasing cAMP concentration.
D. Clopidogrel blocks platelet ADP receptors.
E. Aspirin is a reversible inhibitor of TXA2.

**13. Which of the following pharmacological agents activates plasminogen after binding to fibrin?**
A. Streptokinase
B. Urokinase
C. Alteplase (tPA)
D. Antiplasmin
E. Aminocaproic acid

**14. The major untoward effect of heparin is:**
A. Bleeding
B. Crossing the placenta
C. Elevation of hepatic transaminases
D. Allergic reactions
E. Inhibition of aldosterone synthesis

**15. The lowering of plasma lipids by lovastatin occurs because it:**
A. inhibits HMG coenzyme A (CoA) reductase
B. binds bile acids
C. it inhibits VLDL secretion
D. stimulates HMG CoA excretion
E. increases the activity of lipoprotein lipase

**16. All of the following statements are true EXCEPT:**
A. Heparin acts both in vitro and in vivo
B. Coumarin (warfarin) acts in vivo only
C. Heparin can enter the placenta causing fetal bleeding
D. Coumarin (warfarin) is considered a vitamin K antagonist
E. Heparin must be administered parenterally

**17. Which of the following statements is true concerning cholestyramine?**
A. It inhibits free fatty-acid release from adipose tissue
B. It releases lipoprotein lipase
C. It is an anion-exchange resin that binds bile add in the intestinal lumen
D. It blocks the final step in the formation of cholesterol in the body
E. When used in large doses, it decreases serum cholesterol, triglycerides, and phospholipids, possibly via an effect on synthesis.

**18. Which statement regarding heparin is NOT true:**
A. It inhibits the action of thrombin.
B. Is less effective in-patients with inherited or acquired deficiency of antithrombin III.
C. Is monitored in the laboratory by measurement of activated partial thromboplastin time (APTT).
D. It inhibits antithrombin III.
E. Is reversed by protamine sulfate.

**19. All of the following are recognized adverse effects of heparin EXCEPT:**
A. Osteoporosis.
B. Alopecia.

C. Thrombocytopenia.
D. Allergy
E. Fetal cleft palate.

**20. All of the following inhibit platelet activation and/or aggregation EXCEPT:**
A. Warfarin
B. Eptifibatide
C. Ticlopedine
D. Prostacyclin (PGI2).
E. Dipyridamole.

**21. A 22-year-old woman with deep vein thrombosis in her second trimester of pregnancy, was treated for 7 days with intravenous unfractionated heparin. Which one of the following drugs would be most appropriate outpatient follow-up therapy for this patient?**
A. Warfarin.
B. Aspirin.
C. Alteplase.
D. Unfractionated heparin.
E. Low-molecular-weight heparin (LMWH).

**22. Protamine sulfate administered intravenously to stop heparin-induced bleeding. The mechanism of protamine is:**
A. Degrades the heparin.
B. Inactivates antithrombin.
C. Activates the coagulation cascade.
D. Activates tissue-plasminogen activator.
E. Ionically combines with heparin.

**23. The most important complication of streptokinase therapy is:**
A. Hypotension
B. Bleeding
C. Fever
D. Anaphylaxis
E. Thrombosis

**24. Severe cases of bleeding due to fibrinolytic agents are treated with:**
A. Aspirin
B. Heparin
C. Aminocaproic acid
D. Vitamin K
E. Thromboplastin

**25. Select the most appropriate hypolipidemic drug for a patient with raised LDLcholesterol level but normal triglyceride level:**
A. Simvastatin
B. Clofibrate
C. Probucol
D. Nicotinic acid
E. Thyroxin

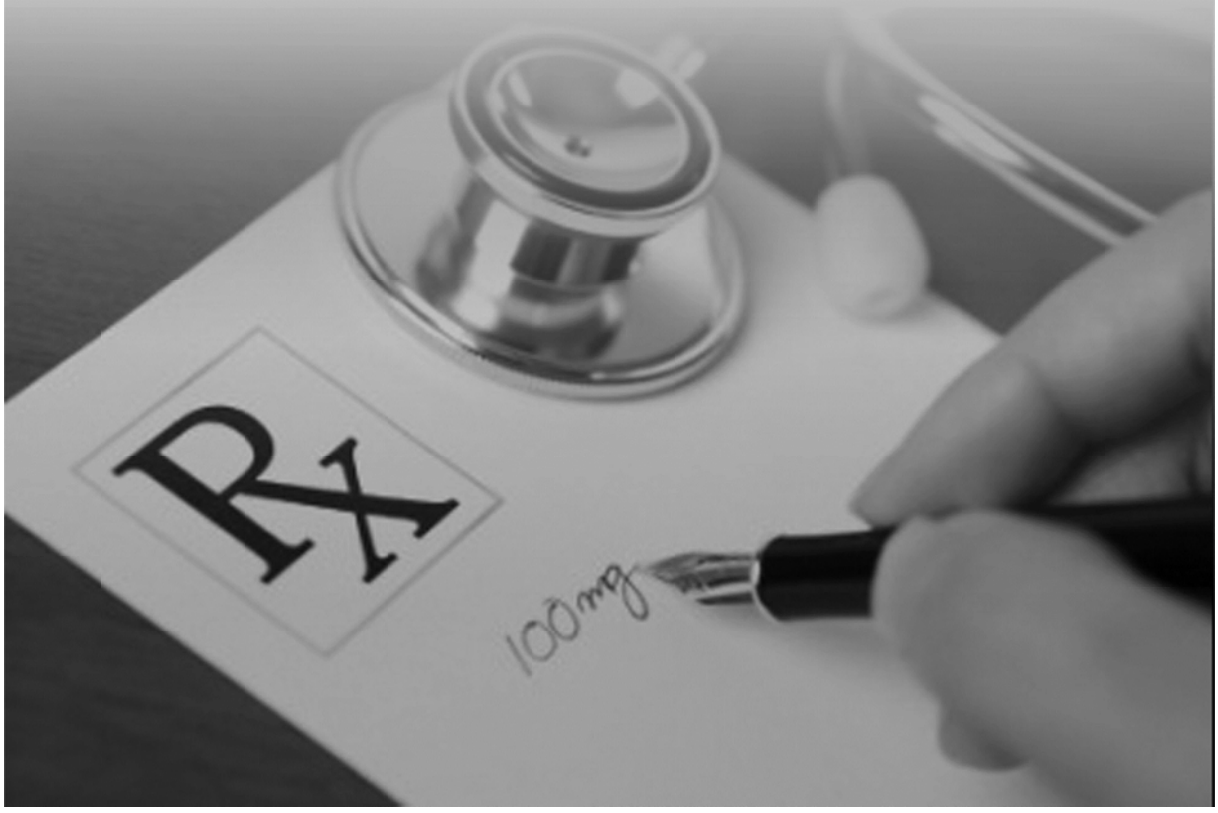
**26. Combined therapy with dipyridamole and warfarin is recommended in subjects with the following:**
A. Risk factors for coronary artery disease
B. Prosthetic heart valves
C. Chronic arteriovenous shunts for repeated haemodialysis
D. Pulmonary embolism
E. Deep vein thrombosis

**Answers**

| | | | | |
|---|---|---|---|---|
| 1 C | 7 B | 13 C | 19 E | 25 A |
| 2 E | 8 D | 14 A | 20 A | 26 B |
| 3 C | 9 E | 15 A | 21 E | |
| 4 A | 10 D | 16 C | 22 E | |
| 5 A | 11 C | 17 C | 23 B | |
| 6 D | 12 E | 18 D | 24 C | |

# Chapter 7

# Respiratory Pharmacology



# Chapter 7

# Pharmacology of the Respiratory System



## Part 1: Agents used to treat cough

### Basic information

- Cough is one of the most common symptoms seen in clinical practice.
- The initial stimulus arises in the bronchial mucosa, where irritation results in stimulation of "Cough" receptors, which are specialized stretch receptors. Afferent impulses reach the cough center in the medulla via the vagus nerve and trigger a cough reflex.
- Cough may be acute (<3 weeks), subacute (3-8 weeks) or chronic (>8 weeks).

**Causes of cough:**

- **Acute cough:** respiratory infection is the most common cause.
- **Chronic cough:**
  - Upper airway cough syndrome (post-nasal drip): due to allergic rhinitis, chronic sinusitis or tonsillitis. It is the most common cause of chronic cough.
  - Bronchial asthma: the 2nd most common cause.
  - Gastoesophageal reflux disease (GERD).
  - Other causes: ACEIs, lung tumors, CHF.

### MANAGEMENT OF COUGH

- **Specific treatment:** directed to the cause of cough e.g. antibiotics for respiratory infections.
- **Non-specific treatment:**
  - **Antitussives:** are used to stop dry cough.
  - **Mucolytics and expectorants:** are used in productive cough to liquefy bronchial secretions and facilitate their removal.

## COUGH SUPPRESSANTS (ANTITUSSIVES)

**Definition:** they are drugs that reduce the frequency or intensity of coughing.

### Peripheral antitussives: they ↓ afferent impulses of the cough reflex.

- **Steam inhalation with menthol or tincture benzoin compound**

– It is one of the best and easy ways to relieve acute cough. Inhaling water steam with or without medications (e.g. menthol) helps flush out mucus and moisturizes dry, irritated air passages. The efficacy of added medication is not proved.

- **Benzonatate**

– It is a glycerol derivative chemically related to the local anesthetic **procaine**. It depresses peripheral cough receptors at the lung by local anesthetic effect.

### Central antitussives: they inhibit cough center in the medulla.

- **Opioids: Codeine and hydrocodone**

– They are *natural* derivatives of morphine. They directly inhibit the cough center in the medulla at doses that are lower than those needed for analgesia.
– They are generally not recommended because of adverse effects.

**Adverse effects**

– **D**rowsiness and constipation.
– Drug **d**ependence if used for long duration.
– Respiratory **d**epression in large doses. Children less than 5 years old are more sensitive to respiratory depression so, codeine is not recommended to children < 5 years.

**N.B.**
Some antihistamines (diphenhydramine) have antitussive activity, the mechanism is unknown. It has undesirable **atropine-like effect** → drying of mucosal secretions.

- **Opioid isomers: Dextromethorphan**

– It is *synthetic* L-isomer of opioids.
– It has selective central antitussive action with **very few** opioid effects (i.e. **less** addiction liability, analgesic action, respiratory depression, or constipation).
– High doses can cause neuropsychiatric effects e.g. sedation and hallucinations.

## MUCOLYTICS

**Definition:** they are agents that reduce viscosity of respiratory secretions without increasing their amount.

### ■ Bromhexine

– Bromhexine acts on the mucus at the formative stages within the mucus-secreting cells. It disrupts the structure of acid mucopolysaccharide fibers in mucoid sputum and produces a less viscous mucus, which is easy to expel.
– Because bromhexine can disrupt the gastric mucosal barrier, it should be avoided in patients with peptic ulcer.

### ■ Ambroxol

– It stimulates synthesis and release of surfactant by type II pneumocytes. Surfactant acts as an anti-glue factor by reducing the adhesion of mucus to the bronchial wall.

### ■ *N*-Acetylcysteine and carbocyseine

– Acetylcysteine has free sulfhydryl (-SH) groups that break disulfide bonds in mucus and reduces its viscosity.
– Unlike acetylcysteine, carbocysteine does not act directly on mucus but rather, it affects the structural components of mucus.

**Therapeutic uses of mucolytics**

- Chronic respiratory diseases: chronic bronchitis, emphysema, bronchiectasis and cystic fibrosis.
- Post-operative and post-traumatic pulmonary complications.
- Chronic sinusitis and chronic otitis media.
- **N.B.** Intravenous *N*-acetylcysteine is used as an antidote for acetaminophen (paracetamol) toxicity (quite apart from its mucolytic activity).

## EXPECTORANTS

**Definition:** drugs that increase water content and amount of the respiratory secretions. This action facilitates the removal of respiratory secretions.

Adequate hydration is the single most important measure to encourage expectoration. Using an expectorant in addition may produce the desired result.

### ■ Potassium iodide

– Iodides accumulates in the bronchial glands and stimulate secretion of low viscosity watery mucous.
– The use of iodides is accompanied by wide range of **side effects** including unpleasant (metallic) taste, increase lacrimal and salivary secretions, painful salivary swelling, hypothyroidism, and skin eruptions (rash).

- **Guaifenesin**

– It is one of the most widely used over-the-counter (OTC) expectorants. It increases bronchial fluid secretions by unclear mechanism.

- **Other expectorants**

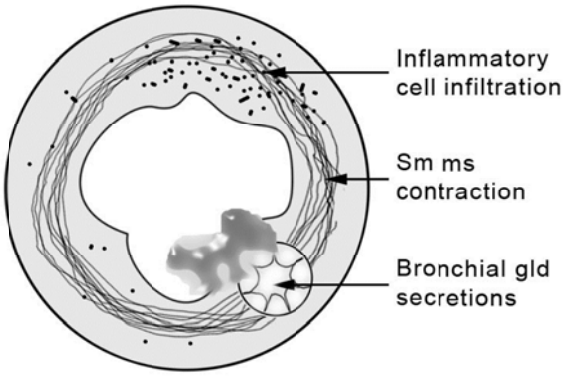
– Many other traditional expectorants (e.g., ammonium chloride, tincture ipecacuanha, herbal remedies) are found in numerous OTC cough mixtures. Their efficacy is doubtful, particularly in the dosages of most preparations.

## Part 2: Therapy of bronchial asthma

**Definition:** *Asthma* is a chronic inflammatory disorder of the airways causing airflow obstruction and recurrent episodes of wheezing, breathlessness**,** chest tightness, and coughing.

### Pathogenesis

Frequent exposure to allergic stimuli causes infiltration of the bronchial wall by acute and chronic **inflammatory cells.** These cells release many **inflammatory cytokines** e.g. histamine, adenosine, PGs, LTs, PAF, etc. leading to:




- Hypertrophy of airway smooth ms
- Increased mucus secretion that is difficult to expel.
- Congestion and edema of the respiratory mucosa.

### Predisposing factors

- **Recurrent respiratory infection:** the most important factor.
- **Genetic factors:** asthma occurs in families with positive history of allergy.
- **Psychological factors:** are present in 40 % of asthmatics.

**Drugs that cause bronchoconstriction in asthmatic patients**

- Cholinomimetic drugs.
- Non-selective β- blockers.
- Histamine releasers e.g. morphine, trimetaphan, curare, penicillins.
- Adenosine
- NSAIDs

### Clinical presentation

- **Chronic asthma**

– There is dyspnea, chest tightness, coughing (particularly at night), and expiratory wheezing.

– Patients can present with mild intermittent symptoms that require no medications or only occasional short-acting inhaled β2-agonists to severe symptoms despite multiple medications.

■ **Acute severe asthma**

– Uncontrolled asthma can progress to an acute state in which inflammation, airway edema, mucus accumulation, and severe bronchospasm that is poorly responsive to bronchodilator therapy.
– There are severe dyspnea, inspiratory wheezing, cyanosis; the patient may be able to say only a few words with each breath.

## MANAGEMENT OF ASTHMA

### BRONCHODILATORS

**3 groups** of bronchodilator drugs:

- **β-adrenergic agonists.**
- **Muscarinic receptor blockers: ipratropium.**
- **Xanthines**: **theophylline.**

### β-adrenergic agonists

#### Classification

- **Non-selective β-receptor agonists:** e.g. adrenaline, isoprenaline and ephedrine. They are rarely used as bronchodilators.
- **Selective β2 agonists:**
  Short acting: salbutamol, terbutaline, fenoterol (duration 3-4 hrs).
  Long acting: salmeterol and formoterol (duration 12 hrs).

#### Mechanism of action

- Stimulation of bronchial $\beta_2$ receptors → ↑ cAMP → bronchodilatation.
- Stimulation of $\beta_2$ receptors in the mast cells → ↓ histamine release
- They ↓ bronchial inflammation and wall edema.

#### Administration

- In acute asthma: short acting $\beta_2$ agonists are given by inhalation or i.v infusion.
- In chronic asthma: long acting $\beta_2$ agonists are given orally or by inhalation.

#### Adverse effects

– **T**achycardia and arrhythmia due to:
  – *Reflex from hypotension (caused by VD of sk ms BV).*

  - *Direct activation of cardiac $\beta_1$ (due to loss of selectivity in high doses).*
- **T**remors of skeletal ms and nervousness.
- **T**olerance with prolonged use *(requiring temporary cessation of the drug).*
- **H**ypokalemia *(due to shift of $K^+$ from blood to cells).*

## Muscarinic antagonists: Ipratropium bromide

- **Atropine** blocks $M_3$ receptors in airway ms leading to bronchodilatation through unopposed $\beta_2$ action, but it is **not used for treatment of asthma** because:
  - It is non-selective $M_3$ blocker leading to many side effects e.g. dry mouth and urine retention.
  - It can cross BBB and causes CNS side effects e.g. sedation.
  - It causes excessive dryness of bronchial secretions making it difficult to expel
- **Ipratropium is more preferred than atropine because:**
  - It is more selective muscarinic blocker than atropine.
  - It is quaternary ammonium compound that can't cross BBB.
  - Does not cause excessive dryness of bronchial secretions.
- **Ipratropium is not sufficient alone for bronchodilatation.** It is usually combined with **$\beta_2$ agonists** to get synergistic effect.

## Methylxanthines

### Classification

- **Natural:** e.g. caffeine, theophylline, and theobromine.
- **Semisynthetic:** e.g. aminophylline (salt of theophylline).

For asthma, the most commonly used xanthine is **theophylline.**

### Mechanism and pharmacological effects

- Xanthines are adenosine **A receptor antagonists** leading to:
  - Bronchodilatation (block bronchoconstrictor effect of adenosine).
  - CNS stimulation (block the inhibitory effect of adenosine on **t**he CNS)
  - ↓ mediator release from mast cells.
  - ↑ AV conduction.
- They inhibit **phosphodiestrase** enzyme (PDE3 and PDE4) → ↑ cAMP leading to:
  - Bronchodilatation (PDE4).
  - ↑ cardiac contractility and arrhythmogenic action (PDE3).
  - VC of cerebral and VD of peripheral vessels.
  - Relaxation of most smooth muscles (GIT, biliary, ureteric, etc).
  - Diuresis.

### Therapeutic uses

■ **Respiratory uses:**

– Acute severe asthma: aminophylline may be given by **slow i.v. infusion** 250 mg i.v. (at least over 15 minutes to avoid syncope or cardiac arrest), followed by maintenance i.v infusion of 0.7 mg/kg/h.
– Chronic bronchial asthma: sustained release tablets of theophylline 100-300 mg/day or rectal suppository of aminophylline can be given.

**Evidence**

In acute asthma, IV aminophylline is not likely to result in any additional bronchodilation compared to standard care with inhaled bronchodilators and steroids.

■ **CNS uses:**

– To reverse CNS depression.
– To delay physical and mental fatigue (caffeine).
– Treatment of migraine (caffeine + ergotamine): to increase VC of cerebral blood vessels and increase absorption of ergotamine from GIT.
– Neonatal apnea syndrome: caffeine is the agent of choice.

■ **CVS uses:**

– Acute pulmonary edema due to acute left sided HF.

### Adverse effects

– **CNS:** irritability, headache, insomnia, nervousness and convulsions.
– **CVS:** palpitations, tachycardia, and arrhythmias. **Rapid i.v. injection** can cause hypotension, syncope and **cardiac arrest.**
– **GIT:** nausea, anorexia, **hyperacidity** and reactivation of peptic ulcer.

### Precautions

- Aminophylline must be given by slow i.v.i. (at least over 15 minutes to avoid sudden syncope or cardiac arrest).
- Used with caution in severe cardiac disease, severe hypoxemia, and renal and hepatic disease and in elderly and neonates.
- They should not be given to patients with peptic ulcer.

### Drug interactions

- **Enzyme inhibitors** (cimetidine and erythromycin) → ↑ serum levels of methylxanthines and ↑ their toxicity (arrhythmia).
- **Enzyme inducers** (smoking, rifampin) → ↓ their serum levels and reduce their effect.

**Evidence**

There is increased risk of arrhythmia when using both β2 agonist and xanthines in the same time because both drugs are arrhythmogenic.

## REDUCTION OF BRONCHIAL INFLAMMATION

### Corticosteroids

**Q**

**Why NSAIDs can not be given in bronchial asthma?**

Because NSAIDs inhibit *Cox* enzyme but NOT *lipooxygenase* enzyme leading to accumulation of LTs which are potent bronchoconstrictors.

#### Mechanism of action

Corticosteroids can effectively ↓ bronchial inflammation and **hyperreactivity** through:

- They inhibit B cell function → ↓ antigen-antibody reaction.
- They inhibit T cell functions → ↓ mediators and cytokine release.
- They inhibit macrophage activity and stabilize lysosomal membranes.
- They inhibit mast cells → ↓ histamine release and capillary permeability.
- They inhibit phospholipase A2 enzyme →↓ synthesis of PGs & LTs.
- Corticosteroids cause up-regulation of β2 receptors.

#### Use in asthma

- Acute severe asthma: **hydrocortisone** 200 mg given by i.v. injection**.** It may be repeated every 4 h if necessary.
- Chronic bronchial asthma: oral **prednisolone** 20 mg/d or **dexamethazone** 4-8 mg/d, or by inhalation (**beclomethasone**).
- **Inhaled corticosteroids (e.g. beclomethazone):** should be considered the 1st choice in newly diagnosed asthma. They have the following advantages:
  - Their efficacy is equal to inhaled $\beta_2$ agonists.
  - Minimal systemic side effects.

#### Adverse effects

- **If used systemically:** …..see endocrine chapter.
- **If used by inhalation:** → **oropharyngeal candidiasis.** It could be avoided by:
  - Mouth wash and gargle after each inhalation.
  - Candida infection can be treated by **nystatin mouthwash** or **amphotricin-B lozenges.**

#### Precautions

- They must be **withdrawn gradually** to avoid acute Addisonian crisis.
- **Diet** should be rich in $K^+$ and proteins and low in NaCl and carbohydrates.
- **Continuous check** for any increase in weight, edema, sugar in urine or BP.
- If the patient develops **acute infection**, he must be treated by adequate antibiotics with decreased dose of steroid.

## PROPHYLACTIC TREATMENT

The following classes of drugs are not bronchodilators but are used to reduce frequency of asthma exacerbations.

### Leukotriene inhibitors:

#### Zafirlukast and montelukast

- They **block leukotriene (LTD4) receptors.**
- Zafirlukast is given twice daily but montelukast is given once daily.

#### Zileuton

- It inhibits 5-lipooxygenase enzyme →↓ leukotriene synthesis.
- Zileuton is microsomal P450 inhibitor and can inhibit the metabolism of many drugs e.g. warfarin and theophylline.

- In clinical trials, leukotriene inhibitors reduced frequency of asthma exacerbations as equal to corticosteroids.
- Montelukast is approved to control asthma in children.

### Mast cell stabilizers:

#### Cromolyn and nedocromil

- Cromolyn sodium (disodium cromoglycate) and nedocromil are poorly soluble drugs and should be given as micronized powder through spinhaler.
- They inhibit mast cell degranulation by unclear mechanism probably by altering the function of **chloride channels** in the mast cell membrane.
- They were used to reduce frequency of attacks **(i.e. prophylactic treatment)** in some allergic conditions e.g. bronchial asthma, allergic rhinitis, and allergic conjunctivitis.
- Their use now becomes **very limited** and has been largely replaced by leukotriene inhibitors.
- **Adverse effects** occur at site of administration e.g. local irritation of the throat, chest tightness, and bronchospasm.

**N.B.**

Mast cell stabilizers are not given during the acute attack. If given during the acute attacks, they may aggravate bronchospasm.

#### Ketotifen

- It is a 2nd generation antihistamine and a mast cell stabilizer.
- It is used as eye drops to treat **allergic conjunctivitis**, and orally as a prophylactic treatment in bronchial asthma and other seasonal allergies.

## OTHER DRUGS USED IN TREATMENT OF BRONCHIAL ASTHMA

- **Expectorants and mucolytics:** to reduce mucus viscosity.

- **Mixture of oxygen (20%) and helium (80%): Heliox**
  - Helium is an inert gas. Its low density facilitates $O_2$ diffusion through obstructed airways → ↓ work of breathing.

- **Anti-IgE monoclonal antibodies: Omalizumab**
  - Omalizumab is a new drug that inhibits the binding of IgE to mast cells and prevents mast cell degranulation. It may also inhibit IgE synthesis by B cells.
  - It reduces frequency and severity of asthma even when the dose of corticosteroids is reduced.

## Stepwise approach for treatment of chronic asthma

The management of stable asthma is now well established with a stepwise approach:

| | |
|---|---|
| Step 1: | Inhaled short-acting B2 agonist (SABA) as required |
| Step 2: | Add inhaled steroid at 400 mcg/day |
| Step 3: | ▪ Add inhaled long-acting B2 agonist (LABA)<br>▪ Still inadequate: continue LABA and increase inhaled steroid dose to 800 mcg/day |
| Step 4: | ▪ increase inhaled steroid up to 2000 mcg/day<br>▪ Add a 4th drug e.g. Leukotriene antagonist, SR theophylline, oral B2 agonist tablets. |
| Step 5: | ▪ Use oral steroid tablet in lowest dose in addition to the high dose inhaled steroid (2000 mcg/day).<br>▪ Refer the patient for specialist care. |

## Treatment of acute severe asthma (status asthmatics)

**Definition:** acute severe asthma (status asthmatics) is a condition in which bronchodilators are poorly effective in relieving the attack.

### Management

- Hospital admission.
- **Oxygen:** to maintain peripheral capillary O2 saturation (SpO2) between 94-98%.

- **β2 agonists:** use high dose by inhalation.
- Add **ipratropium bromide** by inhalation to the β2 agonists.
- **Hydrocortisone:** 200 mg i.v. / 6hs.
- Consider a single dose of **IV magnesium sulphate** (1.2-2 g over 20 min) to patients who failed to respond to initial inhaled bronchodilator therapy.
- Correction of acidosis and dehydration by i.v. fluids.

In acute severe asthma, IV **aminophylline** is not likely to result in any additional bronchodilation compared to standard care with inhaled bronchodilators and steroids.

Routine prescription of **antibiotics** is not indicated for patients with acute asthma.

# Part 3: Oxygen therapy

## Basic information

### Arterial blood gases (ABG): normal values and interpretation

| Parameter | Normal range | Interpretation |
|---|---|---|
| **pH** | 7.34 – 7.44 | – Acidosis ↓ binding of O2 to Hb (tissue hypoxia)<br>– Alkalosis ↑ binding of O2 to Hb. |
| Arterial O2 saturation at ambient air **SaO2** | 94 –100 % | – At open air, SaO2 must be > 94% and PaO2 >80 mm Hg (or 10.6 kPa).<br>– **Hypoxemia** means SaO2 < 90% and/or PaO2 <60 mm Hg (or 8 kPa). At this level, supplemental oxygen should be administered.<br>– At a PaO2 < 30 mmHg, the patient is at risk of death and must be oxygenated immediately. |
| Arterial O2 partial pressure **PaO2** | 80 – 100 mmHg (10.6 –13 kPa) | |
| Arterial CO2 partial pressure **PaCO2** | 35 – 45 mmHg (4.5 – 6 kPa) | – High value (**respiratory acidosis**) denotes hypoventilation problem (e.g. COPD).<br>– Low value (**respiratory alkalosis**) denotes hyperventilation problem. |
| **$HCO3^-$** | 22 – 26 mmol/L | – Low value denotes **metabolic acidosis**.<br>– High value denotes **metabolic alkalosis**. |

**N.B.**

- **Hypoxia:** low oxygen level at the tissues.
- **Hypoxemia:** low oxygen level in the arterial blood.

## OXYGEN THERAPY

### Key points

- Oxygen is stored either in liquid or gaseous form in metal cylinders (green tanks). Oxygen concentrators are also available for long term home use; they extract oxygen from air using electric current.
- Oxygen is commonly delivered to the patient through nasal cannula or face mask.
- Diagnosis of hypoxemia is done either by pulse oximeter (easy) or by arterial blood gas analysis (see table for reference ranges).
- Dyspnea does not necessarily indicate hypoxemia. Severe hypoxemia can be present without dyspnea and vice versa.

Pulse oximeter

### Indications of oxygen therapy

Oxygen should not be used routinely unless there is evidence of hypoxia.

- **Acute hypoxic conditions:** acute MI, acute pulmonary edema, carbon monoxide poisoning, cardiac and respiratory arrest, low COP and metabolic acidosis (bicarbonate <18mmol/L).
- **Chronic hypoxic conditions** (long-term oxygen therapy): e.g. COPD and CHF.

### Monitoring and stopping

- ABG or oximetry should be done within 2 hours of starting oxygen therapy and oxygen delivery is adjusted accordingly.
- Oxygen should be stopped when SaO2 > 92% while the patient is breathing at room air.
- For patients with COPD, the oxygen saturation target should not exceed 92% to avoid CO2 retention (see below).

### Dangers, adverse effects and precautions

- Fire and explosions: (safety measures are required).
- Irritation of nose, pharynx and trachea.
- Inhibition of mucociliary function → ↓ tracheal outflow of mucous.
- CO2 toxicity:

- In patients with COPD who receive supplementary O2, CO2 retention can occur through 2 mechanisms:
  - Increase O2 saturation of blood reduces deoxygenated Hb which carries CO2 in blood (in the form of bicarbonate).
  - In patients with COPD, hypoxia is the main stimulant of respiration (hypoxic drive). If 100% O2 was administered, hypoxia is corrected and the hypoxic drive is lost leading to CO2 retention.
- CO2 retention can lead to headache, drowsiness (narcosis) or even death.
- Prevention: In people with COPD, CO2 toxicity can be prevented by careful control of the supplemental oxygen. Just enough oxygen is given to maintain an oxygen saturation of 88 - 92%.

- Retrolental fibroplasias: high concentration of $O_2$ in neonates (<32 weeks) stimulates fibrous tissue formation posterior to the eye lens and permanent blindness. So, $O_2$ should be used only when needed and its concentration must not exceed 35-40% in premature infants.
- Pulmonary oxygen toxicity: high O2 concentrations (> 60%) given for >48 hours can damage alveolar membrane and cause alveolar edema.

## Notes

Clinical
Pharmacology
Department

Mansoura Faculty of Medicine

## Review Questions

- Discuss different drugs used in the treatment of **cough.**
- Discuss the different lines of treatment of **bronchial asthma.**
- Discuss pharmacology of **xanthenes:** classification, mechanism of action, pharmacologic effects, therapeutic uses, and side effects.
- Mention uses of mucolytics.
- Mention precautions during the use of methylxanthines.
- Mention precautions during the use of corticosteroids in BA.
- Mention the main side effects of oxygen therapy.
- Mention the main side effects of selective beta-2 agonists.
- Mention the main lines of treatment of status asthmaticus.
- Mention 3 drugs causing bronchoconstriction and mention the mechanisms.

**Mention the pharmacodynamic principles underlying the use of:**

– Beta-2 agonists in bronchial asthma.
– Methylxanthines in bronchial asthma.
– Montelukast for prophylaxis of bronchial asthma.
– Acetylcystiene in chronic bronchitis.

**Mention the rationale of the following combinations:**

– Oxygen with helium in chronic obstructive lung disease.
– Corticosteroids with beta-2 agonists in bronchial asthma.

**Of each of the following questions, select ONE BEST answer:**

**1. Which of the following mucolytics act by breaking disulfide bonds of proteoglycans, which causes depolymerization and reduction of viscosity of sputum?**
A. Acetylcysteine
B. Iodides
C. Trypsin
D. Water vapor
E. Licorice

**2. Which of the following drugs is a methylxanthine used in the treatment of bronchial asthma?**
A. Salbutamol
B. Ipratropium
C. Theophylline
D. Pentoxifylline
E. Dipyridamole

**3. The mechanism of methylxanthines action in bronchial asthma is:**
A. Inhibition of the enzyme phosphodiesterase
B. Beta2 -adrenoreceptor stimulation
C. Inhibition of the production of inflammatory cytokines
D. Inhibition of M-cholinoreceptors
E. Inhibition of leukotriene receptors

**4. Which of the following drugs can decrease the effect of leukotrienes in the inflamed tissue?**
A. Zileuton
B. Montelukast
C. Theophylline
D. Loratidine
E. Cromoglycate

**5. Which of the following drugs can decrease the concentration of leukotrienes in the inflamed tissue?**
A. Zileuton
B. Montelukast
C. Theophylline
D. Loratidine
E. Cromoglycate

**6. Indicate the expectorant which increase lung surfactant:**
A. Sodium benzoate
B. Trypsin
C. Ambroxol
D. Tincture Ipecacucnha
E. Iodides

**7. Which one is considered the major side effect of Theophylline:**
A. Bradycardia
B. Arrhythmia
C. Depression of respiratory center
D. Elevation of the arterial blood pressure
E. Depression of mood

**8. Choose the drug belonging to class mast cell stabilizers:**
A. Zileuton
B. Zafirlucast
C. Epinephrine
D. Salbutamol
E. Sodium cromoglycate

**9. Which of the following drugs can disrupt mucus synthesis within bronchial glandular cells?**
A. Potassium iodide
B. Acetylcystiene
C. Bromhexine
D. Trypsin
E. Ambroxol

**10. Which of the following is not a recognized action of terbutaline**?
A. Diuretic effect.
B. Cardiac arrhythmia.
C. Skeletal muscle tremors.
D. Smooth muscle relaxation.
E. Tachycardia.

**11. Disodium cromoglycate has as its major action:**
A. Smooth muscle relaxation in the bronchi.
B. Stimulation of cortisol release by the adrenals.
C. Block of calcium channels in the lymphocytes.
D. Block of mediator release from mast cells.
E. Block of cAMP synthesis in the basophils.

**12. The following may induce bronchospasm EXCEPT:**
A. Propranolol.
B. Morphine.
C. Aspirin
D. Captopril
E. Theophylline.

**13. Which of the following drugs given for cardiovascular indications might complicate the management of asthma in the same patient?**
A. Hydralazine.
B. Verapamil.
C. Nitroglycerine
D. Quinidine.
E. Propranolol.

**14. Methylxanthines:**
A. Cause decreased gastric acid secretion.
B. Are potent diuretics in most patients.
C. Cause increase in mental alertness and even insomnia in some patients.
D. Are potent vasoconstrictors.
E. Cause fatigue of respiratory muscles

**15. Theophylline is therapeutically useful in asthma because:**
A. It has no significant effects on the heart.
B. It stimulates the respiratory center.
C. It increases mediator release from mast cells.
D. It is a potent stimulant of beta-receptors.
E. It increases cAMP without desensitizing receptors in bronchioles

**16. In status asthmaticus, all are true EXCEPT:**
A. Salbutamol and ipratropium may be given by nebulized aerosol
B. IV aminophylline is useful.
C. Hydrocortisone is preferred to prednisolone for initial therapy.
D. Humidified oxygen should be given.
E. Morphine provides useful sedation

**17. All of the following drugs are central antitussives EXCEPT:**
A. Codeine
B. Pholcodeine
C. Noscapine
D. Dextromethrphane
E. Ticture benzoin Co.

**18. In designing a dosage regimen for aminophylline all are true EXCEPT:**
A. Children (ages 3-12 y) have faster clearance of this drug than adults or infants
B. Patients with history of cardiac disease should be carefully monitored, because aminophylline may induce ventricular extrasystoles and other arrhythmias
C. Excessive doses result in skeletal muscle tremors and CNS excitation.
D. The use of tobacco by the patient inhibits the metabolism of aminophylline.
E. Erythromycin increases the serum levels of theophylline.

**19. Ipratropium bromide is:**
A. Derivative of phenylephrine.
B. Less effect on sputum viscosity.
C. Tertiary amine
D. Given by inhalation, oral and parenteral routes
E. More effective bronchodilator than B2 agonist

**20. Disodium cromoglycate, all are true EXCEPT:**
A. Is well absorbed from the GIT.
B. Stabilizes mast cells and prevent their degranulation.
C. Is inhaled as a powder for prophylaxis of bronchial asthma.
D. Can cause bronchconstriction during administration.
E. Can be used in the treatment of allergic rhinitis.

**21. All of the following drugs are mucolytics EXCEPT:**
A. Bromhexine
B. Iodides
C. Acetylcysteine
D. Ambroxol
E. Ketotifen

**22. Oropharyngeal candidiasis is a common side effect of which of the following:**
A. Inhaled beta-2 agonists
B. Inhaled ipratropium
C. Inhaled corticosteroids
D. Inhaled disodium cromoglycate
E. Oxygen

**23. Oropharyngeal candidiasis could be treated by:**
A. Liquorice lozenge
B. Amphotericin-B lozenge
C. Ampicillin
D. Aminoglycosides
E. Steam inhalation

**24. Which of the following statements is NOT true:**
A. Antitussives decrease the amount and liquefy bronchial secretions.
B. Peripheral antitussives are used when the cough arises above the larynx
C. Mucolytics used in the treatment of productive cough to liquefy copious bronchial secretion.
D. Iodides can be used as expectorant and mucolytic
E. Inhalation of water vapor or adequate intake of water is an excellent mucolytic & expectorant.

**25. Combination of B2 agonists and ipratropium can lead to:**
A. Antagonistic effect.
B. Additive effect.
C. Potentiating effect.
D. Synergistic effect.
E. No effect

**26. The Symptoms of allergen-mediated asthma result from which of the following?**
A. Increased release of mediators from mast cells
B. Increased adrenergic responsiveness of the airways
C. Increased vascular permeability of bronchial Tissue
D. Decreased calcium influx into the mast cells
E. Decreased prostaglandin production

**27. Drugs that can dilate bronchi during an acute asthmatic attack include all of the following except**
A. Epinephrine
B. Terbutaline
C. Nedocromil
D. Theophyline
E. Ipratropium

**28. Which of the following is a prophylactic agent that appears to stabilize mast cells?**
A. Aminophyline
B. Cromolyn
C. Epinephrine
D. Ipratropium
E. Metaproterenol

**29. Which of the following has overdose toxicity that includes insomnia, arrhythmias, and convulsions?**
A. Aminophylline
B. Cromolyn
C. Epinephrine
D. Ipratropium
E. Metaproterenol

**30. Which of the following is a very long acting β2 – selective agonist that is used for asthma prophylaxis?**
A. Aminophyline
B. Cromolyn
C. Epinephrine
D. Ipratropium
E. Salmeterol

**31. In the emergency department, the preferred first-line therapy for asthma exacerbation is**
A. Theophyline
B. A beta2-agonist
C. A corticosteroid
D. Cromolyn sodium
E. An antihistamine

**32. A drug administered by inhalation of powder as a prophylactic for asthma**
A. Ephedrine
B. Disodium cromolyn
C. Isoproterenol
D. Ocytriphylline
E. Epinephrine

**33. When administering oxygen to a hypoxemic patient with COPD, the target oxygen saturation level would be:**

A. 94 – 98%
B. 92 – 94%
C. 88 – 92%
D. 60%
E. 100%

**34. Regarding oxygen therapy, one statement is true:**

A. Severe dyspnea does not necessarily indicate hypoxia.
B. Oxygen should be started immediately to all acutely ill patients.
C. Oxygen should be stopped as soon as oxygen saturation reaches 88% in room air.
D. Acidosis increases binding of oxygen to hemoglobin.
E. Oxygen therapy reduces mortality in acute myocardial infarction.

**35. Which of the following drugs given for cardiovascular indications might precipitate bronchospasm in asthmatic patients?**

A. Hydralazine.
B. Verapamil.
C. Nitroglycerine
D. Quinidine.
E. Adenosine.

**Answers**

| | | | | | |
|---|---|---|---|---|---|
| 1 A | 7 B | 13 E | 19 B | 25 D | 31 B |
| 2 C | 8 E | 14 C | 20 A | 26 A | 32 B |
| 3 A | 9 C | 15 E | 21 E | 27 C | 33 C |
| 4 B | 10 A | 16 E | 22 C | 28 B | 34 A |
| 5 A | 11 D | 17 E | 23 B | 29 A | 35 E |
| 6 C | 12 E | 18 D | 24 A | 30 E | |